DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

Eric von Stetten, Ph.D.
Hologic, Inc.
590 Lincoln Street
Waltham, Massachusetts 02154

MAR 1 2 1998

Re: P970017
Hologic Sahara Clinical Bone Sonometer
Filed: April 7, 1997
Amended: April 17, July 1 and 18, August 6, September 15, October 8, November 10 and 13, 1997 and February 4, 1998

Dear Dr. von Stetten:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the Sahara Clinical bone Sonometer. The intended use of the Sahara Clinical Bone Sonometer is to:

> Perform a quantitative ultrasound measurement of the calcaneus (heel bone), the results of which can be used in conjunction with other clinical risk factors as an aid to the physician in the diagnosis of osteoporosis and medical conditions leading to reduced bone density, and ultimately in the determination of fracture risk.
>
> Sahara measures the speed of sound (SOS, in m/s) and broadband ultrasonic attenuation (BUA, in dB/MHz) of an ultrasound beam passed through the calcaneus, and combines these results linearly to obtain the Quantitative Ultrasound Index (QUI). The output is also expressed as a T-score and as an estimate of the Bone Mineral Density (BMD, in g/cm^2) of the calcaneus as measured by Dual Energy X-ray Absorpiometry (DXA).

We are pleased to inform you that the PMA is approved subject to the conditions described below and in the "Conditions of Approval" (enclosed). You may begin commercial distribution of the device upon receipt of this letter.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

CDRH will notify the public of its decision to approve your PMA by making available a summary of the safety and effectiveness data upon which the approval is based. The information can be found on the FDA CDRH Internet HomePage located at http://www.fda.gov/cdrh/pmapage.html. Written requests for this information can also be made to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857. The written request should include the PMA number or docket number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the Federal Food, Drug, and Cosmetic Act (the act).

Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions concerning this approval order, please contact Joseph Arnaudo at (301) 594-1212.

Sincerely yours,

Kimber C. Richter

Kimber Richter, M.D.
Deputy Director
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

Issued: 3-4-98

CONDITIONS OF APPROVAL

APPROVED LABELING. As soon as possible, and before commercial distribution of your device, submit three copies of an amendment to this PMA submission with copies of all approved labeling in final printed form to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration (FDA), 9200 Corporate Blvd., Rockville, Maryland 20850.

ADVERTISEMENT. No advertisement or other descriptive printed material issued by the applicant or private label distributor with respect to this device shall recommend or imply that the device may be used for any use that is not included in the FDA approved labeling for the device. If the FDA approval order has restricted the sale, distribution and use of the device to prescription use in accordance with 21 CFR 801.109 and specified that this restriction is being imposed in accordance with the provisions of section 520(e) of the act under the authority of section 515(d)(1)(B)(ii) of the act, all advertisements and other descriptive printed material issued by the applicant or distributor with respect to the device shall include a brief statement of the intended uses of the device and relevant warnings, precautions, side effects and contraindications.

PREMARKET APPROVAL APPLICATION (PMA) SUPPLEMENT. Before making any change affecting the safety or effectiveness of the device, submit a PMA supplement for review and approval by FDA unless the change is of a type for which a "Special PMA Supplement-Changes Being Effected" is permitted under 21 CFR 814.39(d) or an alternate submission is permitted in accordance with 21 CFR 814.39(e). A PMA supplement or alternate submission shall comply with applicable requirements under 21 CFR 814.39 of the final rule for Premarket Approval of Medical Devices.

All situations which require a PMA supplement cannot be briefly summarized, please consult the PMA regulation for further guidance. The guidance provided below is only for several key instances.

A PMA supplement must be submitted when unanticipated adverse effects, increases in the incidence of anticipated adverse effects, or device failures necessitate a labeling, manufacturing, or device modification.

A PMA supplement must be submitted if the device is to be modified and the modified device should be subjected to animal or laboratory or clinical testing designed to determine if the modified device remains safe and effective.

A "Special PMA Supplement - Changes Being Effected" is limited to the labeling, quality control and manufacturing process changes specified under 21 CFR 814.39(d)(2). It allows for the addition of, but not the replacement of previously approved, quality control specifications and test methods. These changes may be implemented before FDA approval upon acknowledgment by FDA that the submission is being processed as a "Special PMA Supplement - Changes Being Effected." This acknowledgment is in addition to that issued by the PMA Document Mail Center for all PMA supplements submitted. This procedure is not applicable to changes in device design, composition, specifications, circuitry, software or energy source.

Alternate submissions permitted under 21 CFR 814.39(e) apply to changes that otherwise require approval of a PMA supplement before implementation of the change and include the use of a 30-day PMA supplement or annual postapproval report. FDA must have previously indicated in an advisory opinion to the affected industry or in correspondence with the applicant that the alternate submission is permitted for the change. Before such can occur, FDA and the PMA applicant(s) involved must agree upon any needed testing protocol, test results, reporting format, information to be reported, and the alternate submission to be used.

POSTAPPROVAL REPORTS. Continued approval of this PMA is contingent upon the submission of postapproval reports required under 21 CFR 814.84 at intervals of 1 year from the date of approval of the original PMA. Postapproval reports for supplements approved under the original PMA, if applicable, are to be included in the next and subsequent annual reports for the original PMA unless specified otherwise in the approval order for the PMA supplement. Two copies identified as "Annual Report" and bearing the applicable PMA reference number are to be submitted to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850. The postapproval report shall indicate the beginning and ending date of the period covered by the report and shall include the following information required by 21 CFR 814.84:

(1) Identification of changes described in 21 CFR 814.39(a) and changes required to be reported to FDA under 21 CFR 814.39(b).

(2) Bibliography and summary of the following information not previously submitted as part of the PMA and that is known to or reasonably should be known to the applicant:

> (a) unpublished reports of data from any clinical investigations or nonclinical laboratory studies involving the device or related devices ("related" devices include devices which are the same or substantially similar to the applicant's device); and
>
> (b) reports in the scientific literature concerning the device.

If, after reviewing the bibliography and summary, FDA concludes that agency review of one or more of the above reports is required, the applicant shall submit two copies of each identified report when so notified by FDA.

ADVERSE REACTION AND DEVICE DEFECT REPORTING. As provided by 21 CFR 814.82(a)(9), FDA has determined that in order to provide continued reasonable assurance of the safety and effectiveness of the device, the applicant shall submit 3 copies of a written report identified, as applicable, as an "Adverse Reaction Report" or "Device Defect Report" to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850 within 10 days after the applicant receives or has knowledge of information concerning:

(1) A mix-up of the device or its labeling with another article.

(2) Any adverse reaction, side effect, injury, toxicity, or sensitivity reaction that is attributable to the device and

(a) has not been addressed by the device's labeling or

(b) has been addressed by the device's labeling, but is occurring with unexpected severity or frequency.

(3)Any significant chemical, physical or other change or deterioration in the device or any failure of the device to meet the specifications established in the approved PMA that could not cause or contribute to death or serious injury but are not correctable by adjustments or other maintenance procedures described in the approved labeling. The report shall include a discussion of the applicant's assessment of the change, deterioration or failure and any proposed or implemented corrective action by the applicant. When such events are correctable by adjustments or other maintenance procedures described in the approved labeling, all such events known to the applicant shall be included in the Annual Report described under "Postapproval Reports" above unless specified otherwise in the conditions of approval to this PMA. This postapproval report shall appropriately categorize these events and include the number of reported and otherwise known instances of each category during the reporting period. Additional information regarding the events discussed above shall be submitted by the applicant when determined by FDA to be necessary to provide continued reasonable assurance of the safety and effectiveness of the device for its intended use.

REPORTING UNDER THE MEDICAL DEVICE REPORTING (MDR) REGULATION. The Medical Device Reporting (MDR) Regulation became effective on December 13, 1984. This regulation was replaced by the reporting requirements of the Safe Medical Devices Act of 1990 which became effective July 31, 1996 and requires that all manufacturers and importers of medical devices, including in vitro diagnostic devices, report to the FDA whenever they receive or otherwise become aware of information, from any source, that reasonably suggests that a device marketed by the manufacturer or importer:

(1)May have caused or contributed to a death or serious injury; or

(2)Has malfunctioned and such device or similar device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

The same events subject to reporting under the MDR Regulation may also be subject to the above "Adverse Reaction and Device Defect Reporting" requirements in the "Conditions of Approval" for this PMA. FDA has determined that such duplicative reporting is unnecessary. Whenever an event involving a device is subject to reporting under both the MDR Regulation and the "Conditions of Approval" for a PMA, the manufacturer shall submit the appropriate reports required by the MDR Regulation within the time frames as identified in 21 CFR 803.10(c) using FDA Form 3500A, i.e., 30 days after becoming aware of a reportable death, serious injury, or malfunction as described in 21 CFR 803.50 and 21 CFR 803.52 and 5 days after becoming aware that a reportable MDR event requires remedial action to prevent an unreasonable risk of substantial harm to the public health. The manufacturer is responsible for submitting a baseline report on FDA Form 3417 for a device when the device model is first reported under 21 CFR 803.50. This baseline report is to include the PMA reference number. Any written report and its envelope is to be specifically identified, e.g., "Manufacturer Report," "5-Day Report," "Baseline Report," etc. Any written report is to be submitted to:

Food and Drug Administration
Center for Devices and Radiological Health
Medical Device Reporting
PO Box 3002
Rockville, Maryland 20847-3002

Copies of the MDR Regulation (FOD # 336&1336)and FDA publications entitled "An Overview of the Medical Device Reporting Regulation" (FOD # 509) and "Medical Device Reporting for Manufacturers" (FOD #987) are available on the CDRH WWW Home Page. They are also available through CDRH's Fact-On-Demand (F-O-D) at

800-899-0381. Written requests for information can be made by sending a facsimile to CDRH's Division of Small Manufacturers Assistance (DSMA) at 301-443-8818.

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION:

Device Generic Name: Ultrasound Bone Sonometer

Device Trade Name: Sahara Clinical Bone Sonometer

Applicant's Name and Address: Hologic, Inc.
Lincoln Street
Waltham, MA 02154

Premarket Approval Application (PMA) Number: P970017

Date of Panel Recommendation: August 18, 1997

Date of Good Manufacturing Practice Inspection: FEB 25 1998

Date of Notice of Approval of Application: MAR 12 1998

II. INDICATIONS FOR USE:

The intended use of the Sahara Clinical Bone Sonometer is to perform a quantitative ultrasound measurement of the calcaneus (heel bone), the results of which can be used in conjunction with other clinical risk factors as an aid to the physician in the diagnosis of osteoporosis and medical conditions leading to reduced bone density, and ultimately in the determination of fracture risk.

Sahara measures the speed of sound (SOS, in m/s) and broadband ultrasonic attenuation (BUA, in dB/MHz) of an ultrasound beam passed through the calcaneus, and combines these results linearly to obtain the Quantitative Ultrasound Index (QUI). The output is also expressed as a T-score and as an estimate of the Bone Mineral Density (BMD, in g/cm^2) of the calcaneus as measured by Dual Energy X-ray Absorptiometry (DXA).

III. CONTRAINDICATIONS:

The Sahara should not be used to assess patients whose skin is abraded and/or have an open sore in the area that comes into contact with the system.

IV. WARNINGS AND PRECAUTIONS:

The warnings and precautions can be found in the Attachment.

V. DEVICE DESCRIPTION:

The Hologic Sahara Clinical Bone Sonometer performs a quantitative ultrasound measurement of the calcaneus by passing non-audible high frequency sound waves through the heel. From this measurement, the Quantitative Ultrasound Index (QUI), and an estimate of the bone mineral density (BMD, in g/cm^2) of the heel are obtained. The Sahara system is small, light and portable, and plugs into a standard power outlet. Ultrasound measurements are performed on the Sahara system with the patient seated and the foot positioned and secured in the Sahara system using a positioning aide. After the patient's foot is secured, a pair of soft elastomer pads are brought into contact with opposite sides of the patient's heel by means of a motorized caliper mechanism.

Each of the elastomer pads is acoustically coupled to the heel (using an ultrasound coupling gel recommended by Hologic) as well as to a sound transducer, one of which produces the sound waves which are transmitted through the heel and received by the opposite transducer. The ultrasound measurement takes less than ten seconds, after which characteristics of the transmitted sound waves are analyzed automatically and the QUI and estimated heel BMD are calculated. Results are reported on a liquid crystal display (LCD) panel. The ultrasound power levels used by Sahara are lower than the limits for standard imaging ultrasound devices set forth in the "Information for Manufacturers Seeking Marketing Clearance of Diagnostic Ultrasound Systems and Transducers (issued on September 30, 1997)."

The standard Sahara Clinical Bone Sonometer system includes the measurement unit, a foot positioning aide, and accessories. The system is controlled via a keypad on the front of the unit, and operator instructions and examination results are displayed on a built-in LCD panel. A hardcopy printout of measurement results can be obtained via an internal paper strip printer.

In order to provide data storage and reporting features similar to those available on most commercially distributed x-ray bone densitometers, Hologic offers the "Advanced Clinical Option" for the Sahara system. This option consists entirely of software for an external computer which may be connected to the Sahara system via a standard data cable. The Advanced Clinical Option provides a Windows based user interface supporting an electronic patient database for storage of biographical information and measurement results) and report generation capabilities.

A) DEVICE COMPONENTS:

The Hologic Sahara Clinical Bone Sonometer consists of the measurement unit, its power cord/power supply, and a foot positioning aide. Accessories include Sahara ultrasound coupling gel, paper sheets for under the patient's foot ("Sahara ultrasound examination paper"), a quality control phantom, patient report forms, quality control log forms, a training video (The Sahara User Video Guide), the Sahara User's Guide, patient information brochure, physician education materials (The Sahara Physician Learning Series), towelettes, dry wipes, and printer paper for the internal printer.

The Advanced Clinical Option for the Sahara Clinical Bone Sonometer consists of software for an external personal computer, a communications cable, and an Advanced Clinical User's Guide. The external computer and optional external printer that are used with the Advanced Clinical Option may be obtained through Hologic or from a third party, subject to minimum hardware requirements.

B) DEVICE OPERATION:

1) The Sahara Clinical Bone Sonometer:

The Sahara Clinical Bone Sonometer is controlled via a keypad on the front of the unit, and operator Instructions and examination results are viewed on the LCD Display. A hardcopy printout of results can be obtained from per strip printer. This printout reports the QUI and then Estimated Heel BMD (in g/cm^2) and the date and time of the examination, along with preformatted fields for manual entry of patient information. A T-score, based on U.S. Caucasian female reference values is also included on the LCD panel and printout. The T-score may be disabled by the user, or alternatively, user defined local reference values may be entered and used for the T-score computation. A tablet of pre-printed patient report forms are included with the Sahara system for manual recording of patient biographical information and results. These forms also include a graphical plot of the U.S. Caucasian female reference ranges vs. age, allowing the patient's results to be manually plotted for visual interpretation.

2) The Advanced Clinical Software Option:

Through a Windows based interface, the Advanced Clinical interface allows operation of the Sahara unit using a mouse to click on function buttons on the computer screen rather than by using the keypad on the Sahara system. The keypad on the Sahara system remains functional at all times, and the computer/mouse simply provides an alternative to using the keypad.

When using the Advanced Clinical Software, patient biographical information is entered prior to the measurement. This biographical information, and ultrasound measurement results, can be recalled from the database at any time for reporting, archiving, exporting, and/or comparison to results of a follow-up examination. Other than the entering of patient information, the reporting capabilities, and the use of a mouse interface as an alternative to using the keypad on the measurement unit, the operation of the Sahara system is identical with or without the Advanced Clinical software.

C) PRINCIPLES OF OPERATION:

1) Ultrasound Parameters Measured by Sahara:

The ultrasound measurement is performed by transmitting high frequency sound waves through the heel, and characterizing the effects of the heel (in terms of time delay and attenuation) on the incident sound waves. From the signal measured by the receiving transducer, two parameters describing the nature of the sound waves received can be simultaneously determined: Speed of Sound (SOS) and Broadband Ultrasonic Attenuation (BUA).

SOS values are obtained by measuring the time delay incurred by the sound traveling through the heel and the width of the heel, from which the velocity of the sound wave in the heel (in units of meters/second) can be determined. In addition, the attenuation of the sound wave due to the heel can also be measured, and because sound waves of various frequencies are transmitted, the frequency dependence of the attenuation can be determined. The parameter quantifying the frequency dependence of the attenuation is referred to as BUA (in units of decibels/megahertz). Note that for a small percentage of subjects (typically young subjects with high BMD values) the frequency dependence of the attenuation is not linear, and hence the BUA value cannot be estimated with confidence. This condition is automatically recognized by the Sahara system and is indicated on the LCD display.

2) Estimation of Heel BMD from Ultrasound Parameters:

While it has been speculated for many years that the BUA and SOS parameters are sensitive to skeletal parameters other than density (i.e., trabecular structure, elasticity, etc.), the scientific literature has shown that the sensitivity of BUA and SOS to these other parameters is considerably smaller than the sensitivity to density. The fact that the ultrasound parameters are predominantly sensitive to density is shown by the linear correlations observed between Sahara SOS and BUA results and calcaneal BMD as estimated by established x-ray densitometric methods. Because of these linear relationships, it is possible to estimate from the ultrasound result the calcaneal BMD that would be obtained by x-ray techniques. Furthermore, since both BUA and SOS are each linearly related to the x-ray BMD and to each other, these two parameters can be combined (linearly) to improve the estimate of the patient's calcaneal x-ray BMD. Using a simple linear combination, consisting of nothing more than the sum of BUA and SOS with an offset and an overall scale factor, Sahara computes a combined parameter referred to as the Quantitative Ultrasound Index (QUI), similar to what is sometimes referred to in the scientific literature as "stiffness."

The QUI/Stiffness parameter (or BUA or SOS alone) could in principle be used directly for assessment of calcaneal bone status, or it could be transformed (simply by changing the scale) into an "estimated heel BMD" result. Considering the vastly different scales and units for the various parameters (1500-1650 m/s for SOS, 30-150 dB/MHz for BUA, 0.1 - 0.8 g/cm^2 for DXA heel BMD), however, it is clear that to avoid confusion the standard Sahara output parameter should be as simple to understand as possible. Thus to make the Sahara output result more intuitively meaningful to the physician, especially those who may have previous densitometry experience, the Sahara system reports an "Estimated Heel BMD" in units of g/cm.^{2} Because the "Estimated Heel BMD" is obtained from actual measurements of the BUA and SOS parameters (and hence from the QUI/Stiffness parameter), it is also possible to obtain these "raw" ultrasound results from the Sahara system.

VI. ALTERNATIVE PRACTICES / PROCEDURES:

Traditional methods used for the estimation of bone mineral density (BMD) expose the patient and operator to x-ray radiation. These methodologies include single energy x-ray Absorptiometry (SXA), dual energy x-ray Absorptiometry (DXA), quantitative computed tomography (QCT), single photon Absorptiometry (SPA), and dual photon Absorptiometry (DPA). Of these techniques, SXA, DXA, and SPA have been used specifically for the estimation of BMD of the calcaneus.

Of the traditional x-ray based methods for assessing bone density, the Dual Energy X-Ray Absorptiometry (DXA) and Single Energy X-Ray Absorptiometry (SXA) techniques are most widely used. These established techniques estimate BMD at a variety of anatomical sites, including the heel, by measuring the attenuation of x-rays due to passing through the bone.

VII. MARKETING HISTORY:

The Sahara Clinical Bone Sonometer has been marketed in Austria, Australia, Belgium, Brazil, Canada, Chile, Columbia, Costa Rica, Czech Republic, Ecuador, France, Germany, Greece, India, Italy, Japan, Korea, Poland, S. Africa, Switzerland, Taiwan, Thailand, and United Kingdom. The Sahara Clinical Bone Sonometer has not been withdrawn from any international market for any reason related to safety and effectiveness of the device.

VIII. POTENTIAL ADVERSE EFFECTS OF DEVICE ON HEALTH:

There are no known potential adverse effects of this device on health. In fact, this device uses ultrasound power levels lower than standard imaging ultrasound devices which are widely used and accepted . No adverse events have been reported for the Sahara Clinical Bone Sonometer during clinical use, either from the clinical study reported in this submission, or from systems installed internationally.

IX. SUMMARY OF PRECLINICAL STUDIES:

A) LABORATORY STUDIES:

The objectives of the laboratory studies were to document the accuracy of Sahara SOS and BUA measurement results using known standards. The accuracy of Sahara SOS results was tested by measuring a water filled phantom as a function of temperature. Measured SOS values were found to agree closely, i.e. to within 2 m/s, to known water SOS values over a wide range of SOS values (1508 m/s to 1563 m/s) obtained by varying the water temperature from 15.6 to 37.8 degrees Celsius. Note that 2 m/s corresponds to 0.14% of the measurement value, and is smaller than the precision error in vivo (0.22%). Thus these test results confirm the accuracy and linearity of SOS results obtained on the Sahara system to well within acceptable limits. Similarly, the accuracy of BUA measurements was also verified by measurements of water, as water is well known to have a frequency independent attenuation of sound in the 0.2 - 0.6 MHz range, leading to a BUA value equal to zero.

B) ADDITIONAL STUDIES

1) Biocompatibility

Data from a series of in-vitro and in-vivo studies demonstrated the biocompatibility of the following tissue contacting components of the device:
Examination Paper: Standard disposable examination table paper is used. Exam table paper has been used in the U.S. for many years and is regulated as a Class I medical device subject to general controls and exempt from premarket notification requirements.
Painted surface of the U-shaped portion of the foot well: Cytotoxicity, primary skin irritation, and dermal sensitization testing was conducted following good laboratory procedures (GLPs) and using standard accepted protocols. Test results indicated that there were no adverse reactions.
Foam on the underside of the foot positioning aid: A closed-cell flame retardant cross-linked polyethylene foam is used. This material has been used in medical and orthopedic devices for 25 years with no adverse reactions. No testing was done since its safety has been well established.
Transducer pads: skin irritation and sensitization assay testing was conducted following GLPs and using standard accepted protocols. Test results show no adverse reactions.

2) Physics

Hologic provided test data for their transducer, Model S6H434 with maximum values of MI (mechanical index) = 0.003, $I_{spta.3}$ (derated peak spatial-peak, temporal-average intensity) = 7.16E-5 mW/cm_2, $I_{sppa.3}$ (derated spatial-peak, pulse-average intensity) = 0.000116 W/cm_2, and Power = 0.173 W. Additional transducer Models were also tested with similar test results. This intensities are within the limits specified in the CDRH Guidance "Information for Manufacturers Seeking Marketing Clearance of Diagnostic Ultrasound Systems and Transducers" issued on September 30, 1997 for diagnostic ultrasound devices.

3) Electromagnetic Compatibility

Hologic provided evidence showing compliance with the emissions of EMC Directive (89/336/EEC) to the limits of EN Standard 55011 for Group 1 Class B equipment. In addition, the firm provided evidence showing compliance with the immunity requirements of the EMC Directive (89/336/EEC) under the test conditions specified in IEC 801-2:1991, IEC 801-3:Draft, IEC 801-4:1988, and IEC-5:Draft using the criteria specified in EN60601-1-2:1993.

4) Electrical Safety

The device consists of a plastic housing of mechanical, electrical and electronic components. Specific internal components include transducers, motor, computer w/software, position encoder, power supply, keypad w/LCD panel, and a transducer driver. Device conforms to UL 2601-1 Medical Electrical: General Requirements for Safety, CSA C22.2 No 601.1 M90 and EN60601-1990 requirements for patient connected devices. Testing confirmed that this device meets all referenced standards for electrical safety.

5) Software

Software verification tests used to test the Sahara software and Advanced Clinical Option Software were submitted by Hologic and found to be adequate. A hazard analysis indicated that all software and hardware patient and user concerns were adequately addressed. Verification, validation and unit testing demonstrated the device will operate in a manner as described in the specifications.

6) Biological/Sterility

Labeling is provided for cleaning, reuse, warnings, precautions, contraindications, indications for use, prescribing information, and adverse events in the User's Guide. The device is only to be used on intact skin, and the disinfectant used for cleaning is Cavicide, or equivalent, which is EPA registered and FDA cleared for use.

X. SUMMARY OF CLINICAL STUDIES:

The objectives of the clinical studies were to assess the safety and effectiveness of the Sahara Clinical Bone Sonometer in the assessment of skeletal status and risk for osteoporotic fracture.

A) STUDY DESIGN:

1) Introduction and Background:

The safety and effectiveness of the Sahara Clinical Bone Sonometer was investigated in a multi-center clinical trial in which heel BMD, predicted by the Sahara system, was compared to heel BMD estimated by the established standard technique, x-ray densitometry. In order to make a complete and statistically meaningful comparison of Sahara and x-ray heel BMD estimates, the study was designed to recruit subjects into six subject groups specifically defined to insure that heel BMD values spanning the entire clinical range were obtained. Three clinical sites participated in the study.

Results were compared for a total of 247 subjects, demonstrating agreement between heel BMD estimates obtained by Sahara and the DXA technique.

To understand the level of agreement in clinical terms, a comparison of the observed level of agreement for other pairs of accepted and marketed x-ray based techniques for assessing BMD of a given site, for example of the spine or forearm, was made using published data. These comparisons confirm that the level of agreement between Sahara estimated heel BMD and heel BMD estimated by x-ray densitometry are in the range of other accepted x-ray based methods of assessing BMD of the same bone. Furthermore, differences in Sahara estimated heel BMD results between clinically distinct subject groups were similar not only to differences in DXA heel BMD results, but also to those observed for the widely used DXA lumbar spine BMD. Reproducibility of Sahara results was assessed by repeat measurements on all study subjects, demonstrating that the precision error of Estimated Heel BMD obtained by Sahara is clinically acceptable. The safety of the Sahara system was demonstrated, and no adverse events were observed for any study subjects or operators.

Heel ultrasound results were also obtained using the Walker-Sonix UBA-575+ system for 212 of the study subjects. The Walker-Sonix system is similar to the Sahara system, except that the Walker-Sonix system uses a water bath to couple sound to the heel, as opposed to the contact method used by Sahara. The Walker-Sonix system was previously used in a large multi-center prospective fracture risk study, the Study of Osteoporotic Fractures (SOF), in which it was demonstrated that heel ultrasound results are predictive of future fracture.[3] Sahara and Walker-Sonix results were found to be strongly correlated, providing confidence that Sahara results will be similarly sensitive to fracture risk. In order to estimate quantitatively the relationship between Sahara results and risk of future fracture, calculations were performed in which Sahara results were simulated from the SOF Walker-Sonix study data. These simulations indicated that as for Walker-Sonix results, for each population standard deviation decrease in Sahara results there is roughly a doubling of the risk for hip fracture.

From these results it is concluded that QUI, T-score and heel BMD estimates obtained on the Sahara Clinical Bone Sonometer are safe, effective, and clinically useful.

2) Details of the Study Design:

a) Primary Objectives:

- To directly compare Estimated Heel BMD results obtained by the Sahara Clinical Bone Sonometer to those obtained using established x-ray densitometric techniques.
- To assess the reproducibility of Heel BMD results as estimated by the Sahara system.
- To document the safety of the Sahara system.

b) Secondary Objectives:

- To directly compare results obtained by the Sahara Clinical Bone Sonometer to those obtained using the Walker-Sonix UBA-575+ system, which has been shown to be predictive of future fracture risk.
- To compare both qualitatively and quantitatively the differences observed in Sahara and DXA BMD results between clinically distinct subject groups. Inter-group differences were compared, utilizing the exact same subjects, for Sahara BMD results, DXA heel BMD results, and DXA lumbar spine BMD.

c) Subjects:

The Sahara clinical study was carried out at three clinical sites. Caucasian female subjects were recruited into 6 separate groups designed to span the clinical range of calcaneal BMD results from the highest (young adult) to the lowest (extremely elderly) values. All subjects recruited for this study were female Caucasians, as this is the population most susceptible to complications (i.e., osteoporotic fractures) resulting from decreased bone mineral density. However, the relationships between Sahara results and heel BMD assessed by x-ray densitometry are not dependent on race or gender, and therefore heel BMD may be estimated for patients of all races and genders by the Sahara system. Subjects were classified into groups based on age, hip BMD, and fracture status following the accepted clinical classification criteria know as "the World Health Organization (WHO) criteria";

Group 1: Young Healthy (Age range: 25-35 yrs)
Group 2: Elderly Normal (Age range: > 50 yrs, No known maternal history of hip fracture. No history of previous osteoporotic fracture. T-score for femoral neck OR trochanteric BMD $\geq$ -1.0.)
Group 3: Elderly Osteopenic (Age range: $\geq$ 50 yrs. No history of previous osteoporotic fracture. T-score for hip BMD between -1.0 and -2.5)
Group 4: Elderly Osteoporotic (Age range: 50 yrs. T-score for hip BMD < -2.5)
Group 5: Elderly Severely Osteoporotic with previous fractures (Age range: >50 yrs. T-score for hip BMD < -2.5. Positive history of previous Osteoporotic fracture.)
Group 6: Extremely Elderly (Age range: $\geq$ 70 yrs)

DXA and Sahara Ultrasound Procedures Performed on Subjects by Group:
Study procedures performed on subjects enrolled in the Sahara Clinical Study are outlined in Table 1 according to group classification.

Table 1. Procedures performed on study subjects by group classification.

Procedure	Group 1 (n=64)	Group 2 (n=16)	Group 3 (n=50)	Group 4 (n=57)	Group 5 (n=25)	Group 6 (n=35)
Hip DXA*	1 scan†	1 scan	1 scan	1 scan	1 scan	-
Lumbar Spine DXA	1 scan†	1 scan	1 scan	1 scan	1 scan	-
Heel DXA	1 scan	1 scan	1 scan	1 scan	1 scan	1 scan
Sahara Heel Ultrasound	5 msmts.	5 msmts.	5 msmts.	5 msmts.	5 msmts	5 msmts.
Walker-Sonix Heel Ultrasound	3 msmts.	3 msmts.	3 msmts.	3 msmts.	3 msmts.	-

*Note that Hip DXA measurements were performed to classify patients as described in the Inclusion Criteria above.
†Hip and Spine DXA measurements were not performed at one clinical site for the Group 1 subjects due to IRB requirements.

Hip DXA, Heel DXA, Sahara, and Walker-Sonix measurements were performed on the same leg (right) for all subjects, unless fractures were present, in which case all measurements were performed on the opposite (left) leg. DXA BMD scans were performed on Hologic QDR X-Ray Bone Densitometers.

3) Analyses Performed on Clinical Data:

Data was analyzed for 247 subjects, comparing results obtained by the Sahara Clinical Bone Sonometer to heel BMD results obtained by the established DXA technique. The Sahara system measures two parameters: Speed of Sound (SOS, in m/sec), and Broadband Ultrasonic Attenuation (BUA, in dB/MHz), which are combined into a single parameter, the Quantitative Ultrasound Index (QUI/Stiffness).

The QUI/Stiffness parameter, which is linearly related to the DXA heel BMD, is then converted into "Estimated Heel BMD" in units equivalent to DXA heel BMD using the linear relationship determined by the analysis presented below.

The Estimated Heel BMD result is the default output parameter for the Sahara Clinical Bone Sonometer, and therefore the analyses in this section focus on the comparability of this Estimated Heel BMD vs. the heel BMD estimated by the established DXA technique. The conclusions reached apply equally to the QUI parameter as well as to the re-scaled estimated BMD. Note that all study results are quantitative, and as such, there is no potential for bias in interpretation of results.

Statistical analyses were performed to quantify:

a) the parameters (slope and intercept) describing the linear relationship between ultrasound parameters measured by Sahara and heel BMD results obtained by DXA,
b) the relationship between estimated heel BMD obtained from Sahara ultrasound results vs. DXA heel MD was analyzed in terms of a prediction range standard deviation, which describes the r range of the differences between Sahara Estimated Heel BMD and actual heel BMD,
c) the statistical power of the clinical study data with respect to quantifying the relationship between Sahara and DXA estimates of heel BMD
d) the precision of Sahara Estimated Heel BMD,
e) the parameters (slope and intercept) describing the linear relationship between ultrasound parameters measured by the Sahara and the Walker-Sonix systems, and
f) the relationship between Sahara QUI (or equivalently Sahara Heel BMD) and a patient's risk for future fracture.

Relationship between Sahara Results and DXA Heel BMD:

The method of Mandel[5] has been used to analyze the data for the 247 subjects assessed by DXA and Sahara. Because the standard linear regression technique is often used in analyses such as these, ordinary linear regression results were also calculated for the Sahara vs. x-ray heel BMD data. These linear regression results are nearly identical to those obtained by the more powerful Mandel analysis, but do not allow direct calculation of the uncertainty associated with estimating heel BMD with Sahara, and also do not allow the assessment of the statistical power of the calculated uncertainty.

Level of Agreement between Other X-Ray Based Methods of Assessing Bone Density of the Same Anatomical Site:

Published data comparing other accepted and commercialized techniques for assessing bone density of the same anatomical region are presented. All comparisons presented were between different methods of assessing bone density at the same anatomical site. Just as Sahara heel ultrasound results were compared to heel DXA, these analyses focus on the level of agreement between different x-ray based densitometric techniques for assessment of the same bone. Data for these two additional comparisons were analyzed using the same methodology as used for the Sahara vs. DXA comparison

Comparison of the Sensitivities of Sahara Results vs. DXA Results to Changes in Skeletal Status: Data for Clinically Distinct Subject Groups

Following the standard WHO classification criteria, the Sahara clinical study recruited subjects into six clinically distinct subject groups: Young Adult, Elderly Normal, Elderly Osteopenic, Elderly Osteoporotic, Elderly Severely Osteoporotic with Fracture, and Extremely Elderly. For this secondary analysis, Sahara results were compared to DXA Heel BMD and DXA Lumbar Spine BMD results in order to qualitatively and quantitatively compare the sensitivities of the various techniques (via inter-group differences) to changes in clinical status.

Table 2. Revised Group Definitions (following the WHO classification scheme).

Group #	Clinical Classification	Definition	Number Subjects
1	Young Adult	25-35 yrs old	64
2	Elderly Normal	T > -1.0	16
3	Elderly Osteopenic	-1.0 > T > -2.5	50
4	Elderly Osteoporotic	T< -2.5	57
5	Severely Osteoporotic - w/Fracture	T < -2.5 w/ Fracture	25
6	Extremely Elderly	> 70 yrs old	35

Relationship Between Sahara Results and Fracture Risk:

The linear relationship found between Sahara and Walker-Sonix results was used to simulate Sahara results from the SOF study in order to obtain a quantitative estimate of the sensitivity of Sahara results to fracture risk. Sahara results were estimated for each study subject using the slope, intercept, and RMSE describing the relationship between Sahara and Walker-Sonix results. The simulated Sahara results were then analyzed in exactly the same manner as for the original study data, resulting in an estimate of the relative risk for fracture per population standard deviation decrease in Sahara values. Receiver-operator-characteristic (ROC) curves were also constructed to compare the discriminatory abilities of Sahara and Walker-Sonix results. The variability of the simulated Sahara Relative Risk and ROC results was investigated by comparing the results of 11 independent simulations.

4) Results of Analysis of Clinical Study Data:

The relationship between Sahara and DXA heel BMD results is linear, with the average BMD values (for a group of subjects) obtained by either technique being clinically indistinguishable. For individual patients, however, there may be differences between the Sahara Estimated Heel BMD and the DXA Heel BMD. These differences arise due to several factors, including the precision errors inherent in both Sahara and DXA results as well as the subject dependent differences between the ultrasound and DXA measurement methodologies for assessing bone. The 95% confidence interval for differences between Sahara and DXA heel BMD results is ± 2 population SD's, or ± 2 T-scores.

This means that individual patients may be classified differently by Sahara compared to DXA when using the World Health Organization (WHO) classification criteria.[4] The WHO criteria classify patients with BMD values more than 2.5 SD's below the young adult mean (T-score below -2.5) as osteoporotic, and patients with T scores between -1 and -2.5 as osteopenic. However, the differences in T-score results obtained by Sahara and heel DXA are similar to or smaller than the differences found when patients are assessed by any other two accepted methods for assessing BMD of the same anatomical site.[6] For example, the 95% confidence interval is ± 1.8 T-scores for DXA vs. QCT of the spine. Furthermore, the differences for an individual patient assessed at two different anatomical sites can be even larger due to physiological and anatomical differences between the various sites.[6]

It is widely accepted that while any measure of BMD is a strong indicator of risk for osteoporosis and osteoporotic fractures, classification by the WHO criteria is dependent on the measurement technique, and even more so on the measurement site. Note that when using threshold based criteria to classify patients, the continuous exponential increase in fracture risk with decreasing BMD should be considered. Because osteoporosis is a multifactorial disease, consideration of all relevant risk factors (BMD, age, previous fractures, etc.) is also important in the evaluation of a patient.

The relationships between Sahara ultrasound results and heel BMD assessed by the DXA technique are linear, as evidenced by correlation coefficients in the range of 0.82 to 0.85. As well as being correlated to the DXA heel BMD, Sahara BUA and SOS results are also highly correlated to one another (R=0.91). Because of these correlations, it would in principle be possible to estimate the DXA heel BMD from either BUA or SOS alone. It would also be possible to combine the BUA and SOS results together (linearly) to improve the estimate of heel BMD. With this in mind, the Quantitative Ultrasound Index or "QUI/Stiffness" parameter is computed and is similarly correlated (R=0.85) to DXA heel BMD. The relationship between the QUI/Stiffness parameter and the DXA heel BMD has been determined by the method of Mandel,[5] yielding the following linear equation:

$$\textbf{DXA Heel BMD (in g/cm}^2\textbf{)} = \textbf{(Sahara QUI - 12.07) / 158.15}$$

The Sahara system automatically computes the Estimated Heel BMD results for individual patients using this conversion equation, and reports this value on the LCD panel. Note that the linear relationship obtained by the Mandel method is nearly identical to the relationship obtained by standard linear regression.

Prediction Range for estimating DXA Heel BMD from Sahara Ultrasound Results:

The Mandel method provides a means to estimate the standard deviation of the differences between the heel BMD estimated by Sahara and the actual heel BMD. For the Sahara clinical study data, the estimate of this "Prediction Range SD" in units of heel BMD (g/cm^2) was calculated. In order to provide a simple means of interpreting this Prediction Range SD, it has been converted into units of the population standard deviation DXA heel BMD for a typical population (Table 3).

For comparison, the prediction range for estimation of DXA heel BMD from Sahara results is compared in Table 3 to results derived by the identical analysis of published data comparing results obtained by other accepted x-ray methods of assessing BMD of the same anatomical site. The prediction range SD is found to be similar to or superior to that observed for other marketed techniques for assessing the bone mass of the same anatomical site.

Table 3. Data comparing the level of agreement of several marketed and scientifically accepted techniques for assessing density of the same bone. The "Prediction Range" quantifies the uncertainty of a prediction of the result of technique 2 from a measurement made by technique 1. Sahara results are compared to published comparative data for the lumbar spine[6] and the forearm.[7]

Site	Technique 1 (Y)	Technique 2 (X)	R	Prediction Range	(Pred. Range)/ (pop SD)
Lumbar Spine[6]	QCT	Lateral DXA BMD	0.88	0.073 g/cm^2	0.91
Heel	Sahara Est. Heel BMD	DXA Heel BMD	0.85	0.082 g/cm^2	1.03
Forearm[7]	pQCT	DXA BMD	0.74	0.061 g/cm^2	1.22

Comparison of the Sensitivities of X-Ray Densitometry and Ultrasound Results to Differences Between Clinically Distinct Populations:

The clinical data acquired in the Sahara study also allows a comparison of the sensitivities of the various techniques to differences in clinical status. In order to make this comparison, the young healthy adult group (Group 1) was used as a reference. Using a standard method for comparisons between different techniques, the results for each subject were converted into a deviation score (T-score) compared to the mean value for that technique for Group 1. The T-score for each subject was computed by subtracting the Group 1 mean value from the measurement result, and then dividing this value by the population standard deviation value for Group 1.

This T-score comparison is especially useful in situations where techniques with very different mean values and/or ranges are being compared. For example, it would be very difficult to compare heel BMD (values ranging from 0.1 g/cm^2 to 0.8 g/cm^2) to Sahara SOS (values ranging from 1450 m/s to 1620 m/s) because the scales are radically different. By using the T-score approach, the young adult groups of all techniques have the same mean value (zero) and the same range (standard deviation equal to 1 T-score). Clinically, the T-score comparison is also relevant because it allows comparison of the separation and overlap of values obtained in subject groups with different age or disease states.

From this comparison of inter-group differences (Fig. 2) it can be seen that the sensitivity to clinical status is nearly indistinguishable for all ultrasound and x-ray densitometric results at the heel. Furthermore, the sensitivities of all heel estimates are found to be similar to that observed for DXA BMD of the spine. It is of clinical importance to note that the lowest (x-ray) density populations (Group 5 - Severely Osteoporotic with Fracture, and Group 6 - Extremely Elderly) were separated from other populations e—qually well by Sahara results (BUA, SOS, or estimated heel BMD) as by DXA. Average T-scores by group and technique are given in Table 4, indicating quantitatively that Sahara measurement results yield inter-group differences similar to those obtained by accepted x-ray densitometry techniques.

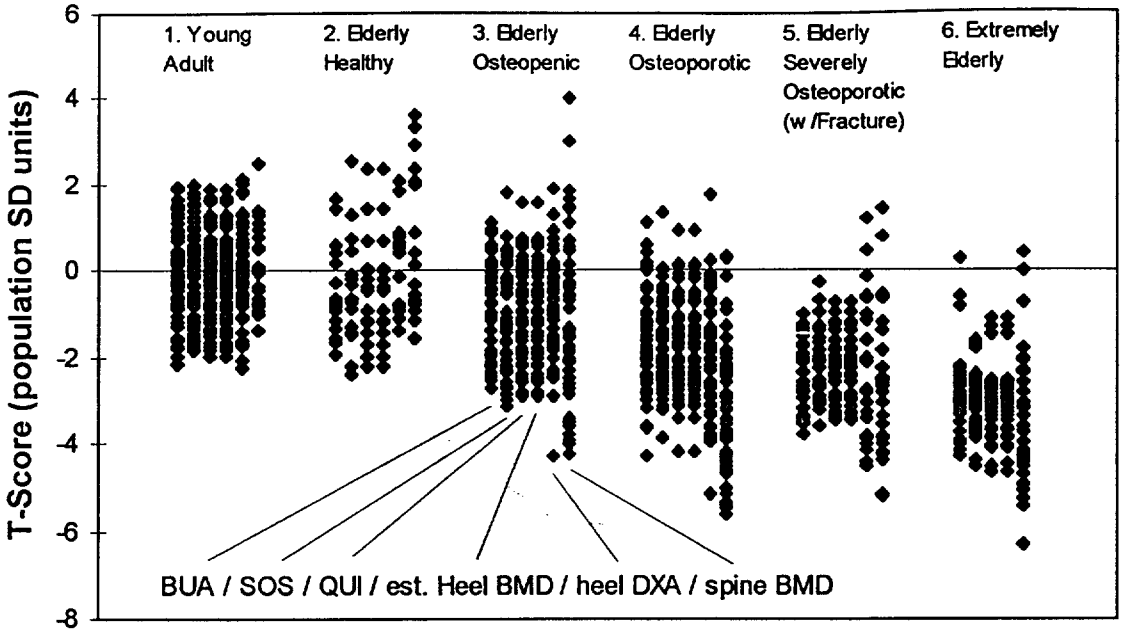

Figure 2. Comparison of Sahara and x-ray densitometry results for the 247 subjects of the Clinical Study. T-scores are computed separately for each technique, using group 1 as a reference. Vertical rows of dots correspond to measurement results for individual subjects with a single densitometric technique (e.g. heel DXA). For groups 1 - 5, results are displayed for six different parameters (left to right): BUA, SOS, Estimated heel BMD, heel DXA, and PA lumbar spine BMD. Note that PA lumbar spine DXA data was not acquired for group 6, leaving only heel DXA, BUA, SOS, and Estimated Heel BMD for this group.

Table 4. Mean T-scores, by technique, for the 247 subjects of the Sahara Clinical Study . The standard error is also reported for each mean T-score.

	Mean T-score (Std Err)					
Technique	Young Adult Group 1 (n=64)	Elderly Normal Group 2 (n=16)	Elderly Osteopenic Group 3 (n=50)	Elderly Osteoporotic Group 4 (n=57)	Severely Osteoporotic Group 5 (n=25)	Extremely Elderly Group 6 (n=35)
Sahara BUA	0.0 (.13)	-0.46 (.27)	-0.77 (.14)	-1.65 (.15)	-2.29 (.17)	-2.87 (.16)
Sahara SOS	0.0 (.12)	-0.49 (.32)	-1.08 (.17)	-1.73 (.13)	-2.18 (.17)	-3.04 (.11)
Sahara Est BMD	0.0 (.12)	-0.50 (.31)	-1.02 (.17)	-1.79 (.14)	-2.33 (.17)	-3.13 (.13)
Heel DXA	0.0 (.12)	0.27 (.29)	-0.81 (.16)	-2.03 (.17)	-2.25 (.31)	-3.50 (.25)
PA DXA	0.0 (.21)*	0.75 (.43)	-1.09 (.27)	-3.27 (.19)	-2.56 (.35)	N/A**

* Note that according to the protocol, PA DXA data was acquired at only one clinical site (23 subjects) for Group I due to IRB requirements.

* PA DXA data not acquired for Group 6.

Statistical Power Analysis:

Statistical power analyses found that the prediction range SD was essentially unchanging for more than 100 - 150 subjects. Thus it was concluded that a clinical study with 100 - 150 subjects would have been sufficient to quantify the relationship between Sahara Estimated Heel BMD and DXA heel BMD, and the 247 subject study presented in this submission therefore has substantially more subjects than required statistically.

Reproducibility of Sahara Estimated Heel BMD Results:

Each of the 247 subjects included in the final clinical study dataset underwent 5 replicate Sahara examinations on the same heel at a single visit, with repositioning between examinations. Of the 247 total subjects, 236 have complete valid data for all 5 examinations, and 11 subjects have between 1 and 4 examinations for which the data is complete and valid. The final precision data comprises 1213 total measurements on 247 subjects.

Precision values were computed (Table 5) for Estimated Heel BMD as well as for the ultrasound parameters (BUA, SOS, QUI/Stiffness). The precision error of the Estimated BMD (0.014 g/cm,^{2} or 3.0%) is significantly smaller than the population standard deviation (0.112 g/cm^2). Thus the precision error of the Sahara Estimated Heel BMD is small enough to allow meaningful assessment of patient status relative to reference ranges.

Table 5. Summary of Precision Results for Sahara Clinical Bone Sonometer

Parameter	SD	C.V.
Est. Heel BMD	0.014 g/cm^2	3.0%
QUI/Stiffness	2.22	2.6%
BUA	2.64 dB/MHz	3.7%
SOS	3.38 m/s	0.22%

Relationship between Sahara and Walker-Sonix Heel Ultrasound Results, Estimated Sensitivity of Sahara Results to Risk of Future Fracture:

a) Correlation between Sahara and Walker-Sonix:

The underlying relationship between Sahara QUI and Walker-Sonix BUA results is strongly linear, with a correlation coefficient of 0.93 between mean Sahara (5 measurements) and mean Walker-Sonix (3 measurements) results. A similarly high correlation (R = 0.91) was found between single measurements on each system. Sahara Estimated Heel BMD, which is obtained by re-scaling the QUI result to put it into units of BMD, is therefore also highly correlated to Walker-Sonix BUA results, with identical correlation coefficients as for QUI.

b) Relative Risk Analysis:

As in the SOF publication presenting Walker-Sonix and x-ray heel BMD results,[3] age adjusted Cox proportional hazard models were used to estimate the relative risk for fracture, including 95% confidence intervals. For each of the 11 independent simulations, an estimate of Relative Risk for future hip fracture per population standard deviation decrease in Sahara results was obtained (Table 6). The 95% confidence interval of relative risk values for all 11 Sahara hip fracture simulations were found to be similar, with a mean relative risk value of 1.840, and an Standard Deviation of 0.13. The relative risk values and confidence intervals were found to be nearly identical to those for Walker-Sonix and x-ray heel BMD results (see Table 6 below)

Table 6. Relative risk results for simulated Sahara data, Walker-Sonix, and X-ray heel BMD, based on data from Bauer et al.[3]

Data	Relative Risk for hip fracture	Relative Risk 95% CI	Width of 95% CI (Upper CL - Lower CL)
Walker-Sonix	2.07	1.50 - 2.86	1.36
X-ray Heel BMD	2.16	1.57 - 2.99	1.42
1st Sahara Simulation	2.041	1.52 - 2.75	1.23
Avg. of 11 Sahara Simulations	1.840 (SD = 0.130)	1.37 - 2.47	1.10

c) Receiver-Operator Characteristic (ROC) Curve Analysis:

Receiver-operator characteristic (ROC) curves were constructed for the simulated Sahara data, the Walker-Sonix data, and also for heel x-ray BMD results. ROC results for Walker-Sonix and heel BMD data were not part of the original publication,[3] and were performed specifically for this analysis. To quantify sensitivity to hip fracture, Area under curve values were computed (Table 7) for each of the 11 Sahara simulations, as well as for the Walker-Sonix and x-ray BMD results. Area under curve values for all 11 simulations were essentially identical, with a mean value of 0.7071 and an SD of 0.0157. These results were also clinically indistinguishable from results for Walker-Sonix (0.713) and for x-ray heel BMD (0.734). The ROC results thus demonstrate not only that Sahara measurements are sensitive to fracture risk, but also show that the sensitivity is essentially identical to that of Walker-Sonix and x-ray heel BMD measurements.

Table 7. ROC Area under the curve results for simulated Sahara data, Walker-Sonix, and x-ray heel BMD, based on prospective hip fracture data from Bauer et al.[3]

Data	ROC Area Under Curve
Walker-Sonix	0.713
X-ray Heel BMD	0.734
1st Sahara Simulation	0.729
Avg. of 11 Sahara Simulations	0.7071 (SD = 0.0157)

Safety of the Sahara Clinical Bone Sonometer:

The safety of the Sahara Clinical Bone Sonometer was demonstrated in the Sahara Clinical Studies where a total of 2255 subjects underwent Sahara examinations without any adverse events. (The total of 2255 subjects includes the 247 subjects from the Sahara vs. DXA comparative study as well as the 2208 subjects from the Sahara reference data study described below.) This clinical experience, combined with the additional clinical experience of Sahara systems distributed internationally, is consistent with the absence of risks determined by a hazard analysis performed on the Sahara system.

5) Reference Ranges for the Sahara Clinical Bone Sonometer:

Age dependent reference ranges for Caucasian American females were developed based on Sahara results for 2208 Caucasian female subjects from ages 19 to 97, who were recruited at 9 clinical centers located across the United States. The large number of subjects and the geographical diversity of the clinical sites minimizes the possibility of statistical or regional bias in the resulting reference ranges. Caucasian female subjects were selected for this reference data study because they are the population most susceptible to complications (i.e., osteoporotic fractures) resulting from decreased bone mineral density, and are by far the population most frequently assessed by bone densitometry. Reference ranges for each Sahara output parameter (Est. BMD, QUI, BUA, and SOS) are based upon the decade specific mean value, and the age-independent pooled population standard deviation obtained from the 2208 subject study.

XI. CONCLUSIONS DRAWN FROM THE STUDIES:

A. RISK/BENEFIT ANALYSIS

All of the x-ray based methodologies for estimating BMD are well established, and there is extensive scientific literature supporting the equivalence and clinical utility of these techniques for assessing bone mineral density of a variety of skeletal sites. It has furthermore been established through large, multi-center, prospective studies that BMD estimates obtained by x-ray densitometry, including heel BMD, are not only sensitive to age and disease related bone loss, but are also predictive of future fracture risk.[1,2,3]

These same prospective studies have also demonstrated that heel ultrasound results, obtained using other devices not commercially available in the United States, are as predictive of future fracture risk as x-ray heel BMD, and approximately as predictive as hip and spine BMD estimated by DXA. Thus the clinical utility of BMD estimates in general, and heel BMD in particular has been well established by alternative (x-ray based) practices. The results of the Sahara clinical study demonstrate the clinical equivalence of Sahara ultrasound estimates of heel BMD and x-ray based heel BMD estimates, and also establishes the relationship between Sahara results and risk of future fracture.

The relationship between Sahara and DXA heel BMD results is linear, with the average BMD values (for a group of subjects) obtained by either technique being clinically indistinguishable. For individual patients, however, there may be differences between the Sahara Estimated Heel BMD and the DXA Heel BMD. These differences arise due to several factors, including the precision errors inherent in both Sahara and DXA results as well as the subject dependent differences between the ultrasound and DXA measurement methodologies for assessing bone. The 95% confidence interval for differences between Sahara and DXA heel BMD results is ± 2 population SD's, or ± 2 T-scores, for an individual patient. This means that individual patients may be classified differently by Sahara compared to DXA when using the World Health Organization (WHO) classification criteria.[4] The WHO criteria classify patients with BMD values more than 2.5 SD's below the young adult mean (T-score below -2.5) as osteoporotic, and patients with T scores between -1 and -2.5 as osteopenic. Differences in T-score results obtained by Sahara and heel DXA are similar to or smaller than the differences found when patients are assessed by any other two accepted methods for assessing BMD of the same anatomical site, and are smaller than those found for an individual patient assessed at two different anatomical sites. Furthermore, while it is widely accepted that while any measure of BMD is a strong indicator of risk for osteoporosis and osteoporotic fractures, classification by the WHO criteria is dependent on the measurement technique, and even more so on the measurement site. When using threshold based criteria to classify patients, the continuous exponential increase in fracture risk with decreasing BMD should be considered. Because osteoporosis is a multifactorial disease, consideration of all relevant risk factors (BMD, age, previous fractures, etc.) is important in the evaluation of a patient.

The ability to estimate heel bone mineral density (BMD) using ultrasound is an important safety advantage of the Sahara Clinical Bone Sonometer compared to other currently marketed modalities, all of which expose the patient and operator to ionizing radiation. Furthermore, the demonstrated relationship between Sahara results and risk of future fracture reinforces the utility of Sahara results to the physician. Due to the extremely low power levels used, the risks posed by the Sahara Clinical Bone Sonometer are also significantly lower than the already minimal risks posed by medical ultrasound devices used for other indications (e.g., imaging). Therefore it is reasonable to conclude that the benefits of the use of the Sahara Clinical Bone Sonometer outweigh the risk of illness or injury when used as indicated in accordance with the directions for use.

B) SAFETY:

A total of 2255 subjects underwent Sahara examinations in the clinical studies without any adverse events. This clinical experience, combined with the additional clinical experience of Sahara systems distributed internationally, demonstrates the safety of the Sahara Clinical Bone Sonometer.

C) EFFECTIVENESS:

The study results and data analysis summarized above demonstrate that Estimated Heel BMD results obtained by the Sahara Clinical Bone Sonometer are equivalent to those obtained by standard x-ray absorptiometric techniques, within clinically acceptable limits. In addition to fulfilling the primary objectives of the clinical study, the data analysis demonstrated that the level of agreement observed between Sahara and DXA heel BMD results is as high or higher than the level of agreement observed for other accepted and marketed x-ray based methods of assessing BMD of the same bone. This result demonstrates that the level of agreement between Sahara and DXA heel BMD results is clinically acceptable, and that Sahara heel BMD estimates can be used for assessment of heel BMD. Furthermore, differences in Sahara estimated heel BMD between clinically distinct subject groups are similar not only to those for DXA heel BMD, but also for those observed for the widely used lumbar spine DXA BMD.

Sahara QUI and Estimated Heel BMD results were found to be strongly correlated to heel ultrasound results obtained by the Walker-Sonix UBA-575+ system, a system which has been shown in the SOF study to provide results that are predictive of future fracture risk. Relative Risk and ROC results obtained by converting Walker-Sonix results from the SOF study into simulated Sahara results indicate that Sahara results are sensitive to risk of future fracture, with approximately a doubling of hip fracture risk per population standard deviation decrease in results. The fracture risk sensitivity found for Sahara is similar to that found by Bauer et al[3] for the Walker-Sonix results and for x-ray based heel BMD results. These relative risk and ROC results are consistent with the cross-sectional data from the Sahara clinical study, which demonstrated similar sensitivity between Sahara, heel DXA, and spine DXA to differences between populations with and without fractures.

The observed similarity in clinical sensitivities observed for Sahara heel BMD, DXA BMD, and Walker-Sonix ultrasound results is consistent with published reports documenting the sensitivity of heel measurements by ultrasound and by x-ray densitometry, and provides further evidence supporting the clinical utility of Sahara estimated heel BMD.

Reference ranges for Caucasian female subjects, obtained in a large, multi-center study, facilitate interpretation of results obtained using the Sahara Clinical Bone Sonometer. The large number of subjects (2208) and clinical sites (9, spread across the United States) contributing data to these reference ranges assures high statistical power and minimal possibility of regional or site specific biases.

Non-clinical testing demonstrated conformance to voluntary safety, electromagnetic compatibility, and quality (ISO) standards. The accuracy of quantitative ultrasound results obtained with the Sahara Clinical Bone Sonometer was documented through measurements performed according to known standards.

XII. PANEL RECOMMENDATION:

At a meeting held on August 18, 1997, the Radiological Devices Panel recommended that Hologic's PMA for the Sahara Clinical Bone Sonometer be approved subject to submission to, and approval by the Center for Devices and Radiological Health (CDRH) of the following:

A) revised intended use statement;

B) revised labeling to include:

- a section on how to interpret the device output for non-white women and men;
- a discussion of the precision of the device and its application for following patients under treatment;
- patient labeling;
- physician labeling; and
- a discussion of the differences in patient classification that may occur with different bone mineral measurement techniques;

C) a labeling section on the normal variations expected for quality assurance measurements; and

D) statistically significant data that demonstrates that the output from your device and the Walker Sonix UBA575 are similar, thus establishing the relationship of your device to fracture risk estimation.

In an amendment received by the FDA on September 15, 1997, Hologic submitted the required information and data. This information adequately addressed the conditions specified by the Panel and the FDA.

XIII. FDA DECISION:

CDRH concurred with the Radiological Devices Panel recommendation of August 18, 1997, and issued a letter to Hologic on September 4, 1997 advising that its PMA was approvable subject to the submission of labeling and data as recommended by the Panel and required by the FDA. The applicant's manufacturing facility was inspected on FEB 25 1998 and was found to be in compliance with the device Good Manufacturing Practice regulations. FDA issued an approval order on MAR 12 1998.

XIV. APPROVAL SPECIFICATIONS:

Directions for use: See the labeling.
Hazards to health from use of the device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the labeling.
Postapproval requirements and restrictions: See Approval Order.

XV. REFERENCES:

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ATTACHMENT

WARNINGS AND PRECAUTIONS FOR THE SAHARA CLINICAL BONE SONOMETER

Warnings:

Prior to using Sahara, users must read "Individualization of Treatment" and "Relationship between Sahara Results and Heel BMD Results obtained by x-ray densitomerty," in the essential prescribing information in order to properly interpret patient results..

Never attempt to operate the Sahara unit with any power module other than the one provided with the system (the Hologic Model Sahara Power Supply). The power supply should only be plugged into a wall outlet that meets all electrical code requirements.

This equipment is not suitable for use in the presence of a flammable anesthetic mixture with air or with oxygen or nitrous oxide.

Precautions:

Use the Sahara Advanced Clinical Bone Sonometer only indoors, in a clean, dry environment.

Do not store the Sahara unit near a heat source or air conditioner. Store the phantom near the unit.

Never store the QC phantom in the footwell with the transducer pads closed on it. This will ruin both the phantom and the transducer pads.

The Sahara Clinical Bone Sonometer provides no protection against the harmful ingress (entry) of liquids.

If at any time the patient feels discomfort during use of the Sahara unit, the foot restraint mechanism is designed to allow the foot to be pulled out without having to operate any levers or handles. The foot could also be removed by using the handles that fully release the foot restraint mechanism. In addition, the Open/Prep button may be pushed at any time to open the transducer pads. Note that in an emergency, it is not necessary to open the pads before removing the patient's foot from the instrument.

Only Hologic approved ultrasound coupling gels should be used with Sahara.

Sahara Ultrasound Coupling Gel is for external use only.

For ultrasound coupling gel application, do not use a Q-Tip, examination glove containing talc, or any other applicator that may introduce fibers or other foreign matter.

When applying gel to the transducer pads, it is important to ensure that the leading edge of the transducer pad is fully covered.

Interfacing equipment (computer, monitor, printer) used with the Sahara Clinical Bone Sonometer must meet IEC 950, or equivalent safety standards.

1

Introduction and Background

This chapter provides overview information about Ultrasound Bone Densitometry and the Sahara Clinical Bone Sonometer. It includes a discussion of ultrasound measurement, safety precautions, system components and product specifications.

Essential Prescribing Information

> *Caution: Federal (U.S.A) Law restricts this device to sale by or on the order of a physician (or properly licensed practitioner).*

1. Device Description:

The Sahara Clinical Bone Sonometer consists of the measurement unit, its power cord/power supply, a foot positioning aide, and accessories. See *How Supplied*, below, for a complete list of accessories.

Ultrasound measurements are performed on the Sahara system with the patient seated and their foot positioned and secured in the Sahara system using a positioning aide. After the patient's foot is secured, a pair of soft elastomer pads are brought into contact with opposite sides of the patient's heel by means of a motorized caliper mechanism. Each of the elastomer pads are acoustically coupled to the heel and to a sound transducer using Sahara Ultrasound Coupling Gel. Inaudible high frequency sound waves, produced by one of the sound transducers, are transmitted through the heel and received by the opposite transducer. Quantitative parameters describing the speed and attenuation of the sound waves in the heel are measured.

The Sahara Clinical Bone Sonometer estimates calcaneal (heel) Bone Mineral Density (BMD, in g/cm^2) from the measured ultrasound parameters. Patient examination time is short, with a measurement time (excluding patient positioning) of less than ten seconds.

2. Intended Use/Indications:

The intended use of the Sahara Clinical Bone Sonometer is to perform a quantitative ultrasound measurement of the calcaneus (heel bone), the results of which can be used in conjunction with other clinical risk factors as an aid to the physician in the diagnosis of

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osteoporosis and medical conditions leading to reduced bone density, and ultimately in the determination of fracture risk.

Sahara measures the speed of sound (SOS, in m/s) and broadband ultrasonic attenuation (BUA, in dB/MHz) of an ultrasound beam passed through the calcaneus, and combines these results linearly to obtain the Quantitative Ultrasound Index (QUI). The output is also expressed as a T-score and as an estimate of the Bone Mineral Density (BMD, in g/cm^2) of the calcaneus as measured by Dual Energy X-ray Absorptiometry (DXA).

3. Contraindications:

- The Sahara should not be used to assess patients whose skin is abraded and/or have an open sore in the area that comes into contact with the system.

4. Warnings:

- Prior to using Sahara, users must read "Individualization of Treatment" and "Relationship between Sahara Results and Heel BMD Results obtained by X-Ray Densitometry," below, in order to properly interpret patient results.
- Never attempt to operate the Sahara unit with any power module other than the one provided with the system (the Hologic Model Sahara Power Supply). The power supply should only be plugged into a wall outlet that meets all electrical code requirements.
- This equipment is not suitable for use in the presence of a flammable anesthetic mixture with air or with oxygen or nitrous oxide.

5. Precautions:

- Use the Sahara Advanced Clinical Bone Sonometer only indoors, in a clean, dry environment.
- Do not store the Sahara unit near a heat source or air conditioner. Store the phantom near the unit.
- Never store the QC phantom in the footwell with the transducer pads closed on it. This will ruin both the phantom and the transducer pads.
- The Sahara Clinical Bone Sonometer provides no protection against the harmful ingress (entry) of liquids.
- If at any time the patient feels discomfort during use of the Sahara unit, the foot restraint mechanism is designed to allow the foot to be pulled out without having to operate any levers or handles. The foot could also be removed by using the handles that fully release the foot restraint mechanism. In addition, the Open/Prep button may be pushed at any time to open the transducer pads. Note that in an emergency, it is not necessary to open the pads before removing the patient's foot from the instrument.
- Only Hologic approved ultrasound coupling gels should be used with Sahara.
- Sahara Ultrasound Coupling Gel is for external use only.
- For ultrasound coupling gel application, do not use a Q-Tip, examination glove containing talc, or any other applicator that may introduce fibers or other foreign matter.

- When applying gel to the transducer pads, it is important to ensure that the leading edge of the transducer pad is fully covered.
- Interfacing equipment (computer, monitor, printer) used with the Sahara Clinical Bone Sonometer must meet IEC 950, or equivalent safety standards.

[redacted]

6. Adverse Events:

There are no known potential adverse effects of the Sahara Clinical Bone Sonometer on health.

- Safety Experience and Sample Size: No adverse events of any kind were reported in the course of the clinical studies performed, in which a total of 2455 subjects underwent Sahara examinations.
- Deaths: There were no patient deaths related to the Sahara Clinical Bone Sonometer either during or after the clinical studies.
- Adverse Events: There were no adverse events related to the Sahara Clinical Bone Sonometer either during or after the clinical studies.
- Adverse Events that may be expected: There are no known potential adverse effects of the Sahara Clinical Bone Sonometer on health. Therefore adverse events are not expected in conjunction with the use of Sahara.

7. Clinical Studies:

- Purpose of Studies: The clinical studies were designed to 1) directly compare estimated heel BMD results obtained on Sahara to those obtained on the established Dual Energy X-ray Absorptiometry (DXA) technique, 2) assess the sensitivity of Sahara heel BMD results to skeletal status vs. that of DXA by comparing results obtained for clinically distinct groups of young and elderly subjects, 3) assess the reproducibility of Sahara heel BMD results, 4) document the safety of the Sahara system, 5) obtain age dependent reference ranges for Sahara estimated heel BMD results for a Caucasian female population, and 6) directly compare Sahara results to those obtained by the Walker-Sonix UBA-575+ heel ultrasound system, establishing the relationship between Sahara and fracture risk estimation.
- Patients Studied: Results for 247 Caucasian female subjects were obtained for the direct comparison of Sahara and DXA heel BMD results. Recruitment criteria were set to insure that these subjects spanned the entire clinical range of heel BMD, with an approximately uniform distribution, in order to document the agreement between Sahara and DXA across the entire useful range. Hip BMD results were used to classify elderly subjects using the internationally accepted World Health Organization (WHO) criteria. Results for 2208 subjects (age range 19-97) were obtained for development of reference ranges. Caucasian female subjects were chosen for these studies as they are the group most frequently affected by osteoporosis.
- Methods: Heel BMD was estimated by Sahara for all subjects, including 5 replicate measurements for the 247 subjects in the comparative study. The 247 subjects from the comparative study also underwent BMD assessment by DXA. Walker-Sonix heel ultrasound results were obtained for 212 of the 247 subjects in the comparative study.
- Principal Effectiveness and Safety Results:

Objective	Result
Comparison of BMD Results vs. Heel DXA	Sahara Est. Heel BMD was linearly related to DXA Heel BMD (R=0.85).
Comparison Sensitivity to DXA	Sahara Est. Heel BMD essentially identical to Heel DXA or comparisons of clinically distinct subject groups. Similar in sensitivity to spine DXA.
Reproducibility of Heel BMD	Est. Heel BMD reproducibility was found to be 3.0% in the 247 subjects studied.
Document Safety	No adverse events were observed (2245 subjects evaluated by Sahara).
Reference Data	Reference data ranges were developed based on 2208 Caucasian female subjects, and are included with standard Sahara system.
Comparison of Results to Walker-Sonix UBA-575+	Sahara QUI and Est. Heel BMD results were linearly related to Walker-Sonix results (R=0.93). A relative risk of 1.84 for hip fracture was estimated for Sahara, based on published Walker-Sonix data.[3]

8. Individualization of Treatment:

The Sahara Clinical Bone Sonometer estimates the Bone Mineral Density (BMD) of the heel. BMD results are used by the physician to assess skeletal status in the evaluation of patients at risk for osteoporosis and other metabolic bone diseases and/or patients who may have reduced bone density due to medical conditions indirectly affecting bone mineral metabolism, medications prescribed for other conditions, heritable or genetic factors, lifestyle factors, or other reasons. Heel BMD results may be used by the physician, along with other factors such as laboratory test results, radiographs, and family history, in the diagnosis of osteoporosis and other conditions leading to reduced bone density.

When evaluating individual patients, all relevant risk factors (including Sahara results, age, previous fractures, frame size, smoking, etc) should be considered. For additional information, refer to the Physician Learning Series included with the Sahara system

The frequency of use of this device to assess BMD is dependent on a number of factors, including the precision of the device and the expected rate of loss or gain in BMD due to disease progression or therapeutic intervention, and must be determined by the physician who is aware of all of these factors. See Chapter 4, *Patient Measurement* for further information regarding monitoring of bone loss with Sahara.

Other than as indicated in the Contraindications and Warnings sections above, there are no specific populations for which Sahara should not be used. Guidelines for the development and use of reference ranges for populations other than Caucasian females (for which reference ranges are supplied by Hologic) are given in Chapter 5 of the User's Guide for the Sahara Clinical Bone Sonometer.

Relationship between Sahara Results and Heel BMD Results obtained by X-Ray Densitometry

Sahara measures the speed of sound (SOS, in m/s) and broadband ultrasonic attenuation (BUA, in dB/MHz) of an ultrasound beam passed through the calcaneus (heel), and combines these results linearly to obtain the Quantitative Ultrasound Index (QUI) and an Estimate of a patient's heel BMD. While ultrasound parameters do not directly measure BMD, BUA and SOS results are correlated (R = 0.82 - 0.85) with heel BMD results obtained by the standard Dual Energy X-ray Absorptiometry (DXA) technique, as are results for the combined QUI parameter (R=0.85). Thus an estimate of heel BMD results is obtained by a simple linear re-scaling of the QUI parameter into heel BMD units (in g/cm^2). The level of correlation (R=0.85) between Sahara and DXA heel BMD results is similar to that observed between other accepted methods for assessing BMD at the same anatomical site.[1] For individual patients, there may be differences between the Sahara and DXA Heel BMD results. These differences arise due to several factors, including the precision errors inherent in both Sahara and DXA results as well as the subject dependent differences between the ultrasound and DXA measurement methodologies for assessing bone. For individual patients, differences between Sahara and DXA heel BMD results have a range equal to one standard deviation (SD) of a typical population of subjects of

the same age. The 95% confidence interval for differences between Sahara and DXA heel BMD results is therefore ± 2 population SD's, or ± 2 T-scores. This means that individual patients may be classified differently by Sahara compared to DXA when using the World Health Organization (WHO) classification criteria.[2] The WHO criteria classify patients with BMD values more than 2.5 SD's below the young adult mean (T-score below -2.5) as osteoporotic, and patients with T scores between -1 and -2.5 as osteopenic. However, the differences in T-score results obtained by Sahara and heel DXA are similar to or smaller than the differences found when patients are assessed by any other two accepted methods for assessing BMD of the same anatomical site.[1] Note that differences for an individual patient when assessed at two different anatomical sites can be even larger due to physiological and anatomical differences between the various sites.[1]

It is widely accepted that while any measure of BMD is a strong indicator of risk for osteoporosis and osteoporotic fractures,[3-5] classification by the WHO criteria is dependent on the measurement technique, and even more so on the measurement site. Thus an understanding of the potential differences in T-score results obtained by different techniques should be considered when applying the WHO classification criteria. When using threshold based criteria to classify patients, the continuous exponential increase in fracture risk with decreasing BMD (see *Relationship Between Sahara Results and Risk of Fracture* below) should be a factor in patient management decisions. Because osteoporosis is a multifactorial disease, consideration of all relevant risk factors is important in the evaluation of a patients. Other risk factors, besides BMD and T-score, include age, previous fractures, frame size, smoking, etc. For example, a 45 year old patient with a T-score of -2.7 and a 75 year old patient with the same T-score of -2.7 have drastically different clinical status, and need to be evaluated appropriately. Similarly, there is no clinical distinction between two patients with T-scores of -2.49 and -2.51 if they have the same age and have no other risk factors. See the Physician Learning Series, included with the Sahara system for additional information.

9. Patient Counseling Information:

Patient Information Brochures are supplied with the Sahara system. These brochures give a brief summary of the importance of bone density testing and information about the Sahara Clinical Bone Sonometer.

10. Conformance to Standards:

There are no known potential adverse effects of this device on health. In fact, this device uses ultrasound power levels lower than standard imaging ultrasound devices which are widely used and accepted. No adverse events have been reported for the Sahara Clinical Bone Sonometer during clinical use, either from the clinical studies or from systems installed internationally.

Non-clinical testing demonstrated conformance to voluntary safety (UL2601-1, EN 60601-1-2 1993, CSA C22.2 No. 601-1-M90), electromagnetic compatibility (EN 55011 Group I Class B, IEC 801-2 1991, IEC 801-3 1984, IEC 801-4 1988) and ISO (ISO 9001) standards.

11. How Supplied:

The Sahara shipping package includes the following:

- One Sahara Ultrasound system
- One Power Supply and One Power cord
- One Positioning aide
- One QC Phantom
- Training Video (The Sahara User Video Guide)
- Starter supplies including:

  Sahara Ultrasound Coupling Gel (2 tubes)
  Transducer Towelettes (1 pkg)
  Dry wipes (1pkg)
  Printer paper (2 rolls)
  Ultrasound exam paper (1pkg)

- Documents package containing:

  User's Guide
  Supplies reorder cards
  Installation, Warranty, and Post Warranty Service Information Sheet
  QC Log Forms (1 tablet)
  Patient Report Forms (1 tablet)
  Patient Information Brochures (1 pkg)
  Sahara Physician Learning Series

12. Operator's Manual:

Attached

13. References:

[1] S. Grampp, H.K. Genant, A Mathur, P. Lang, M. Jergas, M. Takada, C.C. Gluer, Y. Lu, and M. Chavez, "Comparisons of Noninvasive Bone Mineral Measurements in Assessing Age-Related Loss, Fracture Discrimination, and Diagnostic Classification," J. Bone and Miner. Res. Vol 12, pg 697-711, (1997).

[2] Kanis J, et al., Osteoporosis Int. Vol. 4, pg 368-381 (1994).

[3] Bauer DC, Gluer CC, Cauley JA, Vogt TM, Ensrud KE, Genant HK, Black DM. "Broadband ultrasound attenuation predicts fractures strongly and independently of densitometry in older women." Archives of Internal Medicine Vol. 157, pg 629-633, (1997).

[4] Hans D, Dargent-Molina P, Schott AM, et al. "Ultrasonographic heel measurements to predict hip fracture in elderly women: the EPIDOS prospective study." Lancet Vol. 348, pg 511-4 (1996).

[5] Gluer CC, Cummings SR, Bauer DC, et al. "Osteoporosis: association of recent fractures with quantitative US findings." Radiology Vol. 199, pg 725-32 (1996).

Quantitative Ultrasound (QUS) as a Tool for the Assessment of Bone Status

Ultrasound is well established in the medical community as a safe and cost effective diagnostic modality. Until recently, medical ultrasound has primarily given clinicians only qualitative images of soft tissue. However, it is also possible to use ultrasound to obtain quantitative information about bone status. In comparison to traditional techniques for assessment of skeletal status (including radiographs, x-ray absorptiometry, and computed tomography) which involve exposure to radiation, QUS is a quick, low cost, and radiation free diagnostic tool. These advantages are especially important in the clinical environment for which Sahara was designed, where unnecessary operator and patient x-ray exposure (for example) are undesirable.

Many bone diseases, including osteoporosis, degrade cancellous (or trabecular) bone much earlier and to a greater extent than cortical bone. Turnover of cancellous bone is about eight-fold higher than of cortical bone, thus age and disease related bone loss are more readily apparent in cancellous bone compartments. Therefore, it is becoming more widely accepted in the medical community that skeletal sites with a high percentage of cancellous bone are important examination sites for patients at risk for osteoporosis and other metabolic bone diseases. The calcaneus (heel), a bone that is 75-90% cancellous bone by volume and is readily accessible because of the small amount of soft tissue surrounding it, is particularly attractive for studies aimed at the identification and/or assessment of patients at risk. QUS is a modality particularly well suited for the examination of cancellous bone of the heel.

QUS results obtained using the Sahara system are correlated to heel Bone Mineral Density (BMD, in g/cm^2) results obtained by Dual energy X-ray Absorptiometry (DXA), the most widely used technique for assessing BMD. Thus Sahara ultrasound results can be converted into DXA equivalent units (g/cm^2) in order to be more easily interpreted by physicians. The Sahara system therefore reports the "Estimated BMD" of the heel in g/cm^2 as the default output result. Because this Estimated BMD was obtained from ultrasonic measurements, the ultrasound results may also be displayed if desired. Access

to the underlying ultrasound measurement results is especially important for Sahara system Quality Control, where monitoring of the ultrasound parameters is critical for tracking of system performance.

Sahara Clinical System Overview

Sahara is a portable medical instrument that measures the ultrasonic Speed Of Sound (SOS) and Broadband Ultrasound Attenuation (BUA) of the calcaneus (heel), and combines these two measured values to obtain a parameter referred to as the Quantitative Ultrasound Index (QUI), sometimes referred to as "stiffness" in the scientific literature. The QUI/Stiffness value obtained for a patient is then converted into Estimated BMD (in units of g/cm^2) in order to simplify the interpretation of results by the physician. This Estimated BMD is then be compared to reference values in order to assess the bone status of the patient relative to sex and race matched norms. Reference values for United States Caucasian females are supplied with the Sahara system, and it is possible to enter locally derived, user defined reference values in situations where the Caucasian female values may not be appropriate.

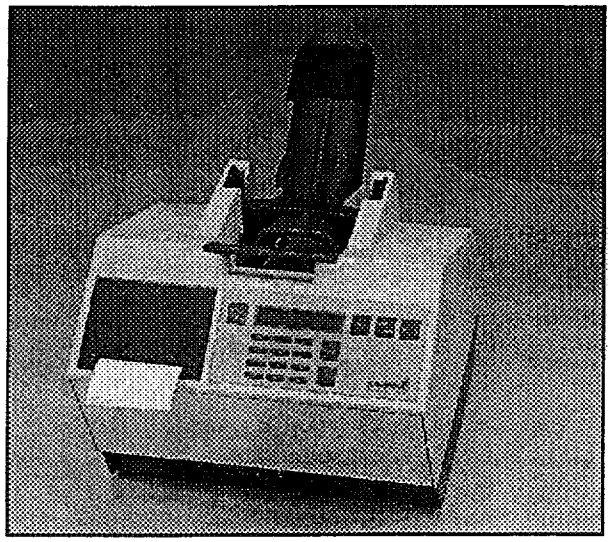
The measurement is taken with the patient seated and their foot positioned and secured in the Sahara system. Soft rubber pads are brought into contact with either side of the heel, and the measurement is performed by passing sound waves through the heel. An ultrasound coupling gel is used between the pads and the patient's skin. No water bath is necessary, and the entire procedure (including patient positioning) takes only a few minutes. Note that the use of coupling gel is critical because it eliminates air at the interface between the pads and the skin, which would otherwise severely inhibit the transmission of sound waves.

> To ensure proper operation, use only the couplant gel provided by Hologic (labeled "Sahara Ultrasound Coupling Gel"). Other gels, particularly those that are water based, will adversely affect system performance, giving inaccurate and/or inconsistent results.

The system design provides for a highly repeatable method of positioning the foot with respect to the measurement device. The lower leg is immobilized by a positioning aid fitted with moldable foam, and a padded strap secures the leg into the positioning aid to set the proper leg angle.

Because the frequency of the sound waves produced by the Sahara system is outside the sensation range of human tissue, patients will not even notice the short pulse of sound waves that are transmitted through the heel for a Sahara measurement.

Figure 1-1
Sahara Clinical System



Ultrasound Measurements Using Sahara

The term ultrasound refers to high-frequency (non-audible) sound waves. Ultrasound measurements are made on the Sahara system by measuring the transmission of these sound waves through the heel. The heel is positioned between a pair of sound transducers (Fig 1-2), with one transducer transmitting the ultrasound signal, and the other transducer receiving the signal after passage through the heel. The transducers are acoustically coupled to the heel by elastomer transducer pads using Sahara Ultrasound Coupling gel, which is applied to the transducer pads. From the signal measured by the receiving transducer, two parameters describing the nature of the received sound waves can be simultaneously determined: Speed of Sound (SOS) and Broadband Ultrasonic Attenuation (BUA).

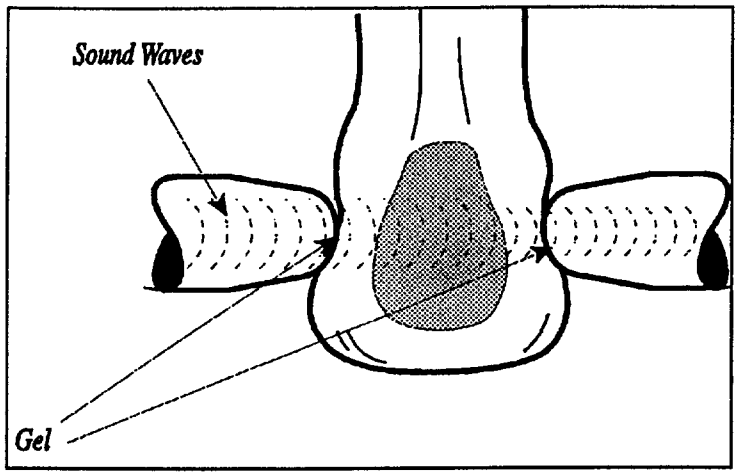
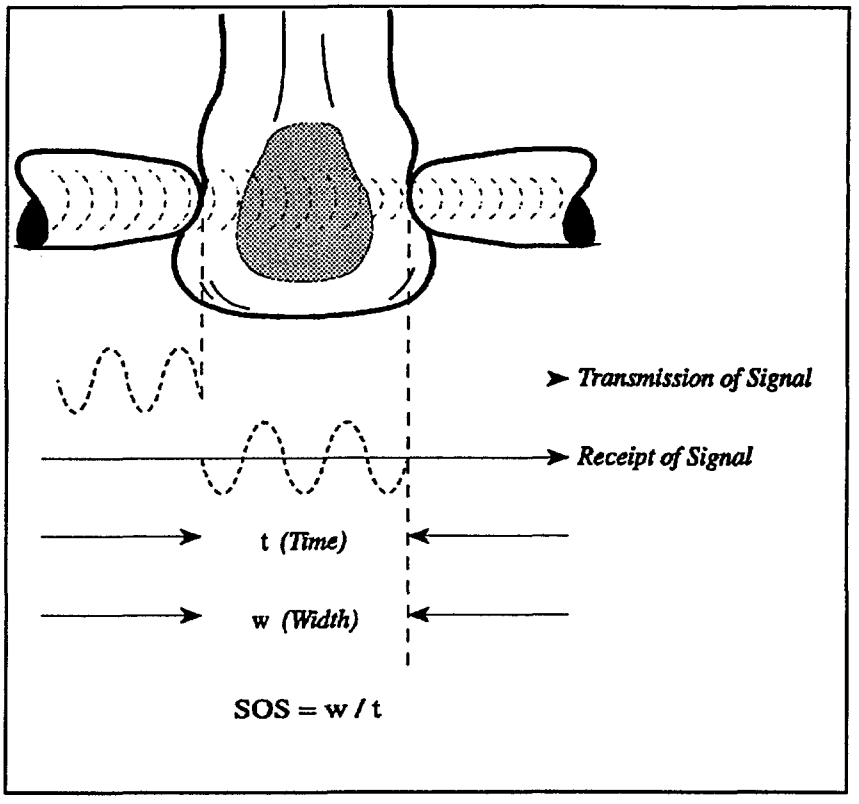


Figure 1-2
Sahara Measurement Geometry

Speed Of Sound (SOS)

SOS is defined as the speed of sound through the heel. SOS is determined (Fig. 1-3) by measuring (1) the width of the heel, and (2) the time delay between the initial transmission of the sound waves (by one transducer) and the receipt of the sound waves (by the second transducer). The Sahara system measures and corrects for the time delay incurred by the sound waves as they travel through the transducer pads by making a similar measurement without the heel (i.e., with the two pads touching one another) in order to determine the time delay due to the heel alone. The time (t) the ultrasound signal takes to go through the heel alone is the propagation time of the ultrasound going through the heel and the transducer pads minus the propagation time measured with the pads touching and with no heel interposed. Sahara automatically measures the width of the heel (w) using a micrometer attached to the transducers. The SOS value is then equal to w/t and is measured in meters per second (m/s). The range observed with Sahara in a typical population is approximately 1450-1700 m/s, with young/healthy subjects having higher SOS values than older or osteoporotic subjects.

Figure 1-3
SOS Measurement



Broadband Ultrasound Attenuation (BUA)

During early investigations of bone with QUS, it was observed that bone attenuated high frequency sound waves much more than low frequency sound waves. A linear relationship (Fig. 1-4) was observed for the attenuation (in decibels, or dB) of ultrasonic waves in the frequency range of 0.2 to 0.6 MHz. The slope of the linear regression of the ultrasonic attenuation vs. frequency in this range is defined to be the broad-band ultrasound attenuation (BUA) and is measured in dB/MHz. On the Sahara system, the BUA and SOS are measured at the same time. As is the case for the SOS measurement, in order to determine the attenuation of the heel alone, and remove any effects arising from the transducers and/or transducer pads, a comparison measurement must be made through a reference medium. This reference measurement is made using the Sahara QC Phantom (supplied with the Sahara unit) when the unit is calibrated at the factory.* The range of BUA observed with Sahara in a typical population is approximately 30-130 dB/MHz, with young/healthy subjects having higher BUA results than older or osteoporotic subjects.

**Note: In the course of typical usage, it is not necessary to perform a reference measurement/calibration. However, if the transducer pads, transducers, or electronics are removed or disassembled for any reason, the unit must be re-calibrated following the instructions in the Maintenance chapter of this manual.*

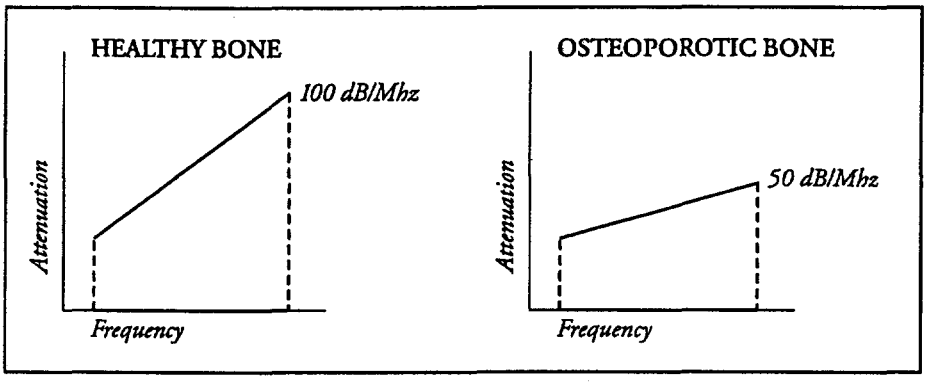


Figure 1-4
BUA Measurement

Estimated Heel BMD and the Quantitative Ultrasound Index (QUI)

In order to optimize the quantitative information obtained by both BUA and SOS measurements, the Sahara system combines (linearly) the two measured values into a single parameter, the Quantitative Ultrasound Index (QUI), sometimes referred to as "Stiffness" in the scientific literature. Compared to the BUA or SOS parameters alone, the combined QUI parameter is both more strongly correlated to the actual heel BMD obtained by the DXA, and also has a reduced precision error. QUI values normally range from 0 to 150, with higher values being obtained for young healthy subjects, and lower values being obtained for older or osteoporotic subjects.

Because the QUI parameter is correlated to heel (DXA) BMD results, a "Predicted" or "Estimated" heel BMD result may be obtained by a simple re-scaling of the QUI value. Thus the re-scaled QUI value ("Estimated Heel BMD, in g/cm^2) is reported by the Sahara system as the default output parameter. Note that the QUI is a simple linear combination of the BUA and SOS, which is formed merely to improve the estimate of heel BMD, the default output of the Sahara system.

Relationship between Sahara Results and Heel BMD Results obtained by X-Ray Densitometry

Clinical studies have compared Sahara results to heel BMD assessed using the established Dual Energy X-Ray Absorptiometry (DXA) technique. These studies have shown that BUA and SOS, the parameters directly measured by Sahara, are correlated (R = 0.82 - 0.85) with DXA BMD. Sahara QUI and Estimated Heel BMD values are also correlated (R=0.85) to DXA BMD results. This level of correlation is similar to that observed between other accepted methods for assessing BMD at the same anatomical site. For example, published studies have shown that standard posteroanterior (PA) DXA lumbar spine BMD results and spine BMD results obtained by the quantitative computed tomography (QCT) technique have in vivo correlations of 0.83.[1]

The relationship between Sahara and DXA heel BMD results is linear, with the average BMD values (for a group of subjects) obtained by either technique being clinically indistinguishable. For individual patients, however, there may be differences between the Sahara Estimated Heel BMD and the DXA Heel BMD. These differences arise due to several factors, including the precision errors inherent in both Sahara and DXA results as well as the subject dependent differences between the ultrasound and DXA measurement methodologies for assessing bone. Subject dependent differences between Sahara and DXA heel BMD results have a range equal to one standard deviation (SD) of a typical population of subjects of the same age. The 95% confidence interval for differences between Sahara and DXA heel BMD results is therefore ± 2 population SD's. T-scores, which quantify the difference between a given patient's results and the mean results for a young adult reference group, are reported in population SD units. Thus patients assessed by Sahara and heel DXA will have results that are equal on the average, but that differ by up to ± 2 T-scores for an individual patient. This means that individual patients may be classified differently by Sahara compared to DXA when using the World Health Organization (WHO) classification criteria.[2] The WHO criteria classify patients with BMD values more than 2.5 SD's below the young adult mean (T-score below -2.5) as osteoporotic, and patients with T scores between -1 and -2.5 as osteopenic. However, the differences in T-score results obtained by Sahara and heel DXA are similar to or smaller than the differences found when patients are assessed by any other two accepted methods for assessing BMD of the same anatomical site.[1] For example, the 95% confidence interval is ± 1.8 T-scores for DXA vs. QCT of the spine. Furthermore, the differences for an individual patient assessed at two different anatomical sites can be even larger due to physiological and anatomical differences between the various sites.[1]

It is widely accepted that while any measure of BMD is a strong indicator of risk for osteoporosis and osteoporotic fractures, classification by the WHO criteria is dependent on the measurement technique, and even more so on the measurement site. Thus an understanding of the potential differences in T-score results obtained by different techniques should be considered when applying the WHO classification criteria. When using threshold based criteria to classify patients, the continuous exponential increase in

fracture risk with decreasing BMD (see *Relationship Between Sahara Results and Risk of Fracture* below) should be a factor in patient management decisions. Because osteoporosis is a multifactorial disease, consideration of all relevant risk factors is important in the evaluation of a patients. Other risk factors, besides BMD and T-score, include age, previous fractures, frame size, smoking, etc. For example, a 45 year old patient with a T-score of -2.7 and a 75 year old patient with the same T-score of -2.7 have drastically different clinical status, and need to be evaluated appropriately. Similarly, there is no clinical distinction between two patients with T-scores of -2.49 and -2.51 if they have the same age and have no other risk factors. Other risk factors, besides T-score and age, include previous fractures, frame size, smoking, etc. See the Physician Learning Series, included with the Sahara system for additional information.

[1] S. Grampp, H.K. Genant, A Mathur, P. Lang, M. Jergas, M. Takada, C.C. Gluer, Y. Lu, and M. Chavez, "Comparisons of Noninvasive Bone Mineral Measurements in Assessing Age-Related Loss, Fracture Discrimination, and Diagnostic Classification," J. Bone and Miner. Res. Vol 12, pg 697-711, (1997).

[2] Kanis J, et al., Osteoporosis Int. Vol. 4, pg 368-381 (1994).

Relationship between Sahara Results and Risk of Fracture

It has been demonstrated in a number of large, multi-center, prospective clinical studies that subjects with low BMD are at higher risk of fracture.[3-5] These studies have found that for elderly Caucasian female subjects (age greater than 70) the risk of future fracture increases exponentially with decreasing BMD. For hip fractures, for example, it was found that for each population standard deviation (SD) decrease in hip BMD, there was a 2 to 3-fold increase in the incidence of fracture. Note that a 2-fold increase in fracture risk per population SD decrease in BMD is referred to as "a relative risk of 2.0." The relative risk result is computed in terms of the difference (in population SD units) between a patient's results and the age matched mean value, which is equivalent to the patient's Z-score. That is, if the relative risk is 2, then a patient with a Z-score of -1 has twice the risk of hip fracture compared to a patient with a Z-score of 0. A patient with a Z-score of -3 has 8 times (2 to the third power) the risk of hip fracture.

The data from the fracture risk studies demonstrates that there is a "gradient of risk," which means that the risk of fracture increases continuously with decreasing BMD. This is in contrast to the "threshold" concept, in which risk suddenly increases below a specific BMD threshold value. Because the results of these and many other studies are consistent with a gradient of risk rather than with a threshold, care must be taken when applying threshold based classification criteria such as those proposed by the WHO. Nonetheless, threshold based guidelines and decision making are in fact commonplace in medical practice even in similar situations (cholesterol testing for example), but should be applied with the understanding that risk is continually increasing above and below the threshold.

The studies found that a similar relationship to hip fracture risk existed for heel ultrasound results, with approximately a 2-fold increase in risk per population SD. In particular, one of the studies included both x-ray based and ultrasound measurements of the heel, and found essentially identical results: the relative risk values for heel ultrasound and heel x-ray BMD were 2.0 and 2.2 respectively.[3] For these studies, heel ultrasound results were obtained using ultrasound systems that use a water bath to couple sound waves to the heel. Sahara is a "dry" heel ultrasound system that uses soft elastomer pads and an ultrasound gel to couple sound to the heel, but is otherwise similar to the "wet" systems used in the fracture risk studies. Data comparing the Sahara and the Walker-Sonix UBA-575+ (the system used in one of the fracture studies) was obtained in the Sahara clinical study. This comparative data demonstrates the strong linear relationship (R=0.93) between Sahara and Walker-Sonix results, which in turn suggests that Sahara results are sensitive to risk of future fracture. In order to estimate quantitatively the sensitivity of Sahara results to risk of fracture, the data from Bauer, et al.[3] were re-analyzed, after using the Walker-Sonix heel ultrasound results to predict Sahara results for all study subjects. In this analysis, Sahara results were estimated using the slope, intercept, and RMSE describing the relationship between Sahara and Walker-Sonix results, as determined in the Sahara clinical study. The estimated Sahara results for all study subjects were then analyzed in exactly the same manner as for the original study data, resulting in a relative risk value of 1.84. Receiver-operator-characteristic (ROC) curves were constructed, indicating that there were no clinically significant differences between the discriminatory abilities of Sahara and Walker-Sonix results.

In summary, large prospective studies have thus demonstrated the strong exponential relationship between heel ultrasound and x-ray results and the risk of fracture. The strong relationship between Sahara and Walker-Sonix results suggests that Sahara results will be equally predictive of fracture risk. For additional information, see the Physician Learning Series included with the Sahara system.

[3] Bauer DC, Gluer CC, Cauley JA, Vogt TM, Ensrud KE, Genant HK, Black DM. "Broadband ultrasound attenuation predicts fractures strongly and independently of densitometry in older women." Archives of Internal Medicine Vol. 157, pg 629-633, (1997).

[4] Hans D, Dargent-Molina P, Schott AM, et al. "Ultrasonographic heel measurements to predict hip fracture in elderly women: the EPIDOS prospective study." Lancet Vol. 348, pg 511-4 (1996).

[5] Gluer CC, Cummings SR, Bauer DC, et al. "Osteoporosis: association of recent fractures with quantitative US findings." Radiology Vol. 199, pg 725-32 (1996).

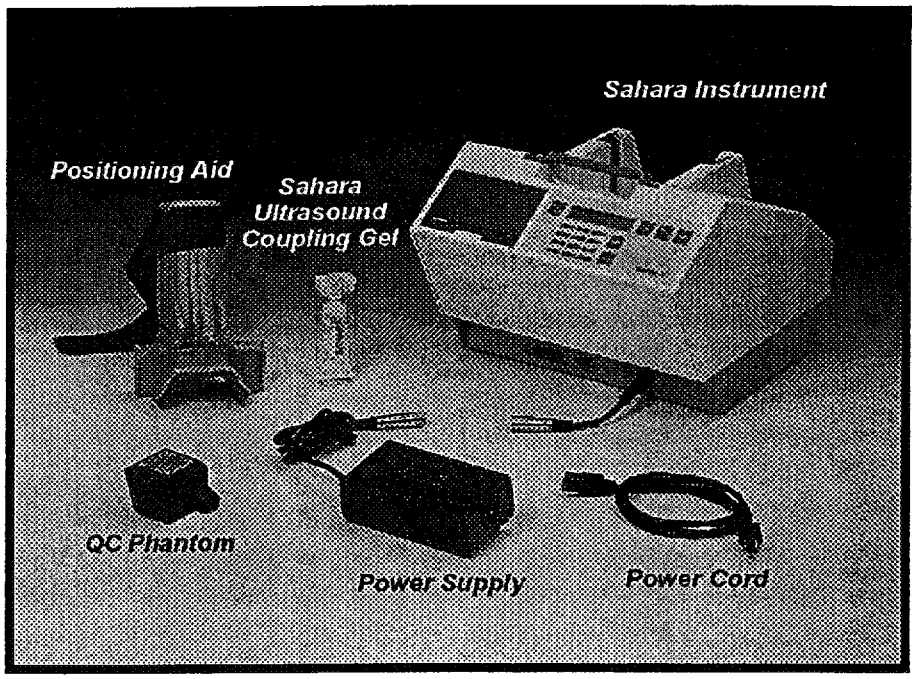
System Components

The key components of the Hologic Sahara Clinical Bone Sonometer system are shown in Figure 1-5, including the ultrasound unit, foot positioning aid, power supply, power cord, QC phantom, and Sahara Ultrasound Coupling Gel. A thermal dot matrix printer contained within the Sahara system is used to provide a printout of measurement results. Quality Control Log sheets provide a means for recording and tracking QC results over time, and Patient Report Forms are provided for recording of patient biographical information and measurement results.

A complete list of accessories and supplies for the Sahara Clinical Bone Sonometer is given in the Essential Prescribing Information above, and also in Chapter 2 of this User's Guide.

Optional software, called the **Advanced Clinical Software Option**, is also available. This software, when installed on an external PC, provides a data base for storage and retrieval of patient records. For operator convenience, the instrument may be controlled using a mouse from the computer, rather than by pressing the keys on the Sahara unit. In addition, full size patient reports including patient history can be obtained. This software option may be installed at any time before or after system installation, as each Sahara system has a standard communication port installed at the factory for communication with the optional Advanced Clinical Software/computer. Contact Hologic for more information.

Figure 1-5
System Components



Quality Control (QC) Phantom

The QC phantom supplied with the Sahara system serves two distinct purposes:

1. Daily measurements of SOS and BUA using this phantom allows monitoring of system performance over time. See the Quality Control chapter, in this manual, for more information.
2. The QC phantom is used to calibrate the Sahara system for BUA and SOS measurement in the event of malfunction, or if the transducers, transducer pads, or electronics are removed or replaced for any reason.

Note: The QC phantom should be stored with the unit but not in the heel well. The phantom and pads can both be ruined by long term contact with each other.

Ultrasound Coupling gel

The Sahara Clinical Bone Sonometer requires the use of a special couplant gel that is supplied with the unit. Standard ultrasound coupling gel will not provide the specified performance level. To ensure proper operation, use only the couplant gel provided by

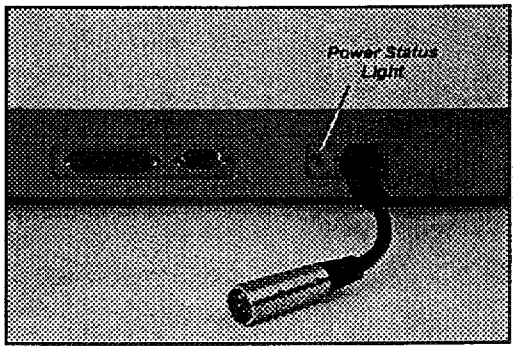
Hologic (labeled "Sahara Ultrasound Coupling Gel"). Other gels, particularly those that are water based, will adversely affect the measurement results. Information on ordering Sahara Ultrasound Coupling Gel can be found in the Maintenance chapter of this manual.

Controls and Indicators

This section describes the controls and indicators on the Sahara Control Panel.

The power status light is located at the rear of the system near the power connection. This light will illuminate when power is applied to the unit. Note that the Sahara system does not have an on/off switch. Power is applied by plugging in the power module.

Figure 1-6
Power Status Light



The Control Panel, shown in Figure 1-7, contains a display screen, numeric keypad and five functional switches.

Figure 1-7
Control Panel

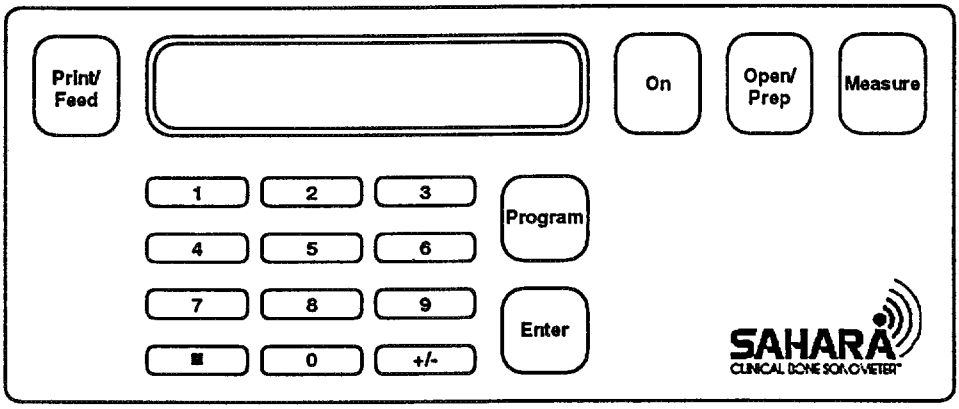


Table 1-1 describes the functions on the Sahara Control Panel.

Table 1-1 Control Panel

Control	Description
Numeric Keypad	The Numeric Keypad consists of the numbers 0 through 9, the Program and Enter buttons. These are used to enter phantom information and other numeric data. The Numeric Keypad is not normally used during patient measurements.
LCD Screen	The LCD display screen displays messages to prompt the user through a measurement, and displays the result of a measurement.
ON Button	This button takes the system out of standby mode, or initializes the system to prepare for a new measurement.
OPEN/PREP Button	This button places the transducer pads in the Open (fully open), or Prepare (half open), positions, and may be used to open the pads anytime they are closed, or are closing.
MEASURE Button	This button commands the system to close the transducer pads and perform an ultrasound measurement.
PRINT/FEED Button	This button commands the system to print the current results or advance printer paper if the optional line printer is supplied.
Program Button	This button is used to inform the Sahara that program information (such as setting the local time and date) will follow.
ENTER Button	This button is used to initiate functions entered with the PROGRAM and Numeric Keypad.
+/- Button	This button allows the user to toggle between Estimated BMD results and QUI/BUA/SOS results after a measurement. It is also used in the PROGRAM mode to alter numeric sign and select choices.

Specifications

IEC 601-1 Class 1 Type BF. IPX0. The UL classification for the Sahara Clinical Bone Sonometer is Class 1 Equipment. Table 1-2 lists the specifications for the Sahara clinical system.

Table 1-2
Sahara Specifications

Measurement Site:	Calcaneus (heel)
Coupling Method:	Sahara Coupling Gel only
Measurement Time:	less than 10 seconds
Patient Reports:	Built-in Strip Printer
Measurement Results:	Estimated Heel BMD and Quantitative Ultrasound Index (QUI), obtained from measured BUA and SOS
Estimated Heel BMD	
C.V.:	3%
Absolute Precision:	0.014 g/cm^2
QUI	
C.V.:	2.6%
Absolute Precision:	2.2
SOS	
C.V.:	0.22%
Absolute Precision:	3.4 m/s
BUA	
C.V.:	3.7%
Absolute Precision:	2.6 dB/MHz
QC Check:	Daily, utilizing supplied QC phantom
Operating temperature range:	60° - 100° F (15° - 37.7° C)
Operating humidity range:	20-80% R.H. non condensing
Shipping and Storage:	
Ambient Temperature	-40° to 120° F (-40° C to 49° C)
Relative Humidity	20% to 95%
Atmospheric Pressure	500 hPa to 1060 hPa
Power Requirements:	100-240 VAC, 50-60 Hz, <60 watts (automatically adjusts from 100 VAC to 240 VAC, and 50 Hz to 60Hz)
CPU	Embedded microprocessor
Ultrasonic Energy:	I_{sppa} < 0.001 W/ cm^2 typical I_{spta} < 0.001 mW/ cm^2 typical Mechanical Index (MI) < 0.01 typical Pulse Repetition Rate (PRR) < 200 Hz
Safety Standards:	IEC601-1, UL2601-1, CSA C22.2
Size:	17"D x 14"W x 12"H (43cm x 36cm x 30cm)
Weight:	22 lb. (10 kg)